Multicenter pilot study of radio-chemotherapy as first-line treatment for adults with medulloblastoma (NOA-07)

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DOI: https://doi.org/10.1093/neuonc/nox155

Neuro-Oncology

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--Manuscript Draft--

Manuscript Number:	N-O-D-17-00180R2
Full Title:	Multicenter pilot study of radio-chemotherapy as first-line treatment for adults with medulloblastoma (NOA-07)
Article Type:	Clinical Investigations
Keywords:	Medulloblastoma, radio-chemotherapy, health-related quality of life, cognition, imaging
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Abstract:	Background: Medulloblastoma in adult patients is rare, with 0.6 cases per million. Prognosis depends on clinical factors and medulloblastoma entity. No prospective data on the feasibility of radio-chemotherapy exist. The German Neuro-Oncology Working Group (NOA) performed a prospective descriptive multicenter single-arm Phase II trial to evaluate feasibility and toxicity of radio-polychemotherapy. Methods: The NOA-07 trial combined cranio-spinal irradiation with vincristine, followed by eight cycles of cisplatin, lomustine and vincristine. Adverse events, imaging and progression patterns, histological and genetic markers, health-related quality of life (HRQoL) and cognition were evaluated. Primary endpoint was the rate of toxicity-related treatment terminations after four chemotherapy cycles, and the toxicity profile. The feasibility goal was reached if at least 45% of patients received at least 4 cycles of maintenance chemotherapy. Results: Thirty patients were evaluable. Each 50% percent showed classic and desmoplastic-nodular histology. Sixty-seven percent were classified into the sonic hedgehog (SHH) subgroup without TP53 alterations, 13% in wingless (WNT), and 17% in Non-WNT/Non-SHH. Four cycles of chemotherapy were feasible in the majority (n=21; 70.0%). Hematological side effects and polyneuropathy were prevalent toxicities. During the active treatment period, HRQoL and verbal fluency improved significantly. The 3-year event-free survival rate (EFS) was 66.6% at the time of databank lock. Conclusions: Radio-polychemotherapy did lead to considerable toxicity and a high amount of dose reductions throughout the first four chemotherapy cycles that may affect efficacy. Thus, we propose frequent patient surveillance using this regimen. Modifications of the regimen may increase feasibility of radio-polychemotherapy of adult patients with medulloblastoma.

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To
Prof. P. Wen
Editor-in-Chief

Neuro-Oncology

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Aktenzeichen	Unser Zeichen	Bearbeiter	Telefon	Regensburg,
		P. Hau	09 41 941-8083	18.07.2017

Second Re-submission with major revisions - Ms. No. N-O-D-17-00180R1

Dear Prof. Wen,

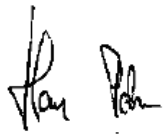
many thanks for the opportunity to, for the second time, re-submit our above mentioned manuscript to Neuro-Oncology with *major revisions*.

Below, you will find our point-to-point answer to all reviewer comments. Please be aware that there are two open questions where we will need the feedback of the acting editor and the reviewer, respectively.

We declare that our manuscript, or any part of it, has not been previously published or submitted concurrently to any other journal, and that all co-authors have read and approved the revised version of the manuscript. We further declare that we agree to pay for full color reproduction.

We hope that the revisions will now qualify the manuscript for publication in Neuro-Oncology. We will however be happy to address further questions, if indicated.

With best regards,



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		P. Hau	09 41 941-8083	18.07.2017

Second Re-submission with major revisions - Ms. No. N-O-D-17-00180, N-O-D-17-00180R1

With respect to reviewer #2, we made the following changes:

"The authors have adequately responded to all of the reviewers' comments and critiques, and included appropriate modifications within their manuscript."
Answer: Many thanks for this positive and supportive statement.

"There are a few minor errors in the Tables which need amending: (1) Table 1 - the KPS ratings appear to be incorrectly labeled; there are gaps between the ratings. (2) Table 2 - M2/3 patients number 9, while Table 3 indicates 10 (does the tenth include a single patient both M2 and M3?) this discrepancy needs clarification. (3) Table 3 - resection is described as "not applicable" -surely the authors mean "not available"?
Answer: we carefully reviewed these statements. Concerning error (1), the ratings were KPS 100, n=8 (26,7%), KPS 90, n=15 (50,0%), KPS 80, n=2 (6,7%), KPS 70, n=3 (10,0%), KPS 60, n=1 (3,3%), KPS 50, n=1 (3,3%), KPS 40-0, n=0 (0.0%) in more detail. We revised table 1 accordingly. Concerning error 2, we listed n=10 patients with M2 or M3-disease in table 2. Therefore, we were not able to detect a discrepancy in between data. If we should have overlooked the point the reviewer wanted to make, we would ask the reviewer to indicate the problem in more problem. Concerning error 3, we thank the reviewer for this comment and corrected the wording in "data not available".

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With respect to reviewer #3, we made the following changes:

"The manuscript by Dagmar Beier and Colleagues has been extensively reviewed by the authors following the suggestions of the reviewers."
Answer: We thank the reviewer for this positive comment.

"However, a crucial point remains, since authors did not answer satisfactory to one of the crucial topics, which regards the statistical design of their study. It is obvious that the backbone of a study is the statistical plan that has some rules to warrant that the study may provide reliable answers. The authors mentioned that they looked at "the minimal number of patients required" but the decided arbitrary that the number of patients was 30, without any statistical plan. To demonstrate the importance of a statistical plan that takes into account factors such as H0, H1, alpha, beta, drop-out rate, etc. Authors found a high level of attrition, in a small cohort of patients. Thus, despite this study is of interest, the results are strongly limited and potentially biased. Authors are invited to clearly describe these biases in the discussion and to clarify across the text that this is a prospective "descriptive" study, as they mentioned in their answer."
Answer: The goal of this study was to evaluate, whether the addition of cytotoxic agents to the standard treatment of adult medulloblastoma is feasible without unacceptable toxicity in a prespecified number of patients according to published literature [1]. This hypothesis results in an exploratory and descriptive feasibility design, focusing on the rate of toxicity-related treatment terminations after 4 cycles of adjuvant chemotherapy. The statistical approach of this study therefore did not contain a formal H0/H1 hypothesis, which would be mandatory if any comparison of efficacy between standard treatment and intervention was the primary purpose. In contrast, the primary endpoint was defined by the hypothesis that more than 60% of the treatment population will complete four cycles of maintenance therapy without toxicity-related treatment terminations. Conceivably, this could be formulated as HO/H1 hypothesis, i.e. H0 would indicate that 60% or more patients show excessive toxicity leading to termination of cytotoxic treatment, which would indicate that the primary endpoint has not met and this treatment is not feasible. This methodology is widely accepted and has been utilized in a number of phase I trials [2]. Therefore, we do not assume that our approach will lead to a significant bias of the results in our study. However, to follow the recommendation of the reviewer, we included a statement in the discussion that this is a prospective descriptive study and stated the same more clearly in several other sections of the manuscript. We did not include a description of H0 at this time, as this was not described in the prospective statistical plan of the study. However, if recommended by the reviewer, we could include: "H0 would indicate that 60% or more patients show excessive toxicity leading to termination of cytotoxic treatment, which would indicate that the primary endpoint has not met and this treatment is not feasible" in the methods section.

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"Moreover, the authors now included the sentence : "17 of 30 patients (56.7%) would receive at least four cycles of maintenance chemotherapy, or 44.3% would not be terminated before four cycles were concluded (p1)" which is not clear, Authors should clarify."

Answer: We thank the reviewer you for this helpful comment, since the wording of this sentence is in fact unclear. In this study, the primary endpoint was defined by a maximal rate of toxicity related treatment termination rate of 60% after 4 cycles of chemotherapy, which in a study population of 30 patients would equal 18 patients. The hypothesis was, that less than these 18 patients (60%) would show treatment related toxicity leading to treatment termination. Therefore, if maximally 17 patients would have to terminate treatment due to toxicity (56.7%) the primary endpoint would be met. We have changed the sentence into: "… we hypothesized that if the study population consists of 30 patients, and less than 18 patients (60%) or maximally 17 patients (56.7%) would have to terminate treatment due to toxicity, the primary endpoint would be met".

"In the CONSORT the "per protocol" population is 25 patients. Five patients were excluded, 2 of these patients were excluded due to toxicity. Authors are invited to highlight data about these 2 patients and the reasons why they were excluded. The remaining 3 patients were excluded due to patients wish (that probably means withdrawal of informed consent). When did these patients retire the consent?"

Answer: Thank you for this comment. We went back to the data to describe these events more precisely. All 5 patients were excluded after termination of radio-chemotherapy. Open tuberculosis with paralytical ileus and sepsis due to pneumonia were severe adverse events terminating treatment in each one patient. Two patients were lost because they withdrew informed consent, and one patient changed to a local institution after radio-chemotherapy, which was not registered as study site. We also added this information to the revised version of the paper.

"In table 3 - authors should define if the results were calculated in the "per protocol population" or in the "intent-to-treat" population."

Answer: The results described in table 3 were calculated in the "intent to treat population".

"Supplemental tables 2a/b should be included in the full text (and not only online)"

Answer: many thanks for the suggestion. Supplementary table 2 contains only one part. In the current version of the paper, we have already outnumbered the allowed number of tables and figures according to Neuro-Oncology style. We would therefore leave to the editor if he/she finds it appropriate to include more tables in the main paper text and will be happy to change that if suggested by the editor.

"Regarding the point raised by the Authors: "We are unsure if this reviewer's information is correct. In our own meta-analysis in adults and in line with data e.g. from Alba Brandes, "only" about 15-20% of the relapses occurred 5 years after diagnosis". The paper by A.A. Brandes (Cancer 2007) clearly stated that: "the risk of

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recurrence appeared to increase markedly after 7 years of follow-up in low-risk patients and after 10 years of follow-up in high-risk patients."

Answer: Many thanks for this remark. We now mention both (contradictory) statements from our own and the Brandes paper in the discussion section of the new paper version.

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2. Wong KM, Capasso A, Eckhardt SG. The changing landscape of phase I trials in oncology. *Nat Rev Clin Oncol.* 2016; 13(2):106-117.

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N-O-D-17-00180R1

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Running title:

Radio-chemotherapy for adults with medulloblastoma

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Funding:

This work was supported by internal grants of the German Neurooncology Society (NOA); and an unrestricted educational grant from medac GmbH.

The sponsors had no influence on study design, in the collection, analysis, and interpretation of data, in the writing of the report and in the decision to submit the paper for publication. The corresponding author had full access to all the data in the study and had full responsibility for the decision to submit for publication.

Conflict of interest:

None related to the work presented here.

Total manuscript word count:

~~5883~~5430.

Abstract

Background: Medulloblastoma in adult patients is rare, with 0.6 cases per million. Prognosis depends on clinical factors and medulloblastoma entity. No prospective data on the feasibility of radio-chemotherapy exist. The German Neuro-Oncology Working Group (NOA) performed a prospective descriptive multicenter single-arm Phase II trial to evaluate feasibility and toxicity of radio-polychemotherapy.

Methods: The NOA-07 trial combined cranio-spinal irradiation with vincristine, followed by eight cycles of cisplatin, lomustine and vincristine. Adverse events, imaging and progression patterns, histological and genetic markers, health-related quality of life (HRQoL) and cognition were evaluated. Primary endpoint was the rate of toxicity-related treatment terminations after four chemotherapy cycles, and the toxicity profile. The feasibility goal was reached if at least 45% of patients received at least 4 cycles of maintenance chemotherapy.

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Conclusions: Radio-polychemotherapy did lead to considerable toxicity and a high amount of dose reductions throughout the first four chemotherapy cycles that may affect efficacy. Thus, we propose frequent patient surveillance using this regimen. Modifications of the regimen may increase feasibility of radio-polychemotherapy of adult patients with medulloblastoma.

Key words:

Medulloblastoma, radio-chemotherapy, health-related quality of life, cognition, imaging

Importance of the study:

NOA-07 showed that combined radio-chemotherapy followed by maintenance chemotherapy with cisplatin, lomustine, and vincristine is more toxic in adults than in children. This prospective descriptive trial constitutes a unique dataset that perpetuates the development of effective treatments in this curable population. The results have potential to influence or even change clinical practice. The NOA-07 protocol can be translated to the recommendation that adults with medulloblastoma should be treated with attenuated radio-polychemotherapy regimen that consider the decreased feasibility of radio-polychemotherapy in adults in comparison to children. In addition, an attenuated NOA-07 regimen may serve as a basis for the standard arm in a subsequent trial. Current knowledge makes it likely that such a trial will ask a molecular question in its experimental arm and will lead into a molecularly stratified approach for adults with medulloblastoma.

Introduction

Medulloblastoma is rare in adults. About 70% of cases occur in patients younger than 15 years [1]. The US SEER database reports 0.6 cases per million in adults per year [2]. Five-year overall survival depends on clinical prognostic factors [3], and on histological entity and genetic subgroup [4], and reaches 40-90%. Long-term sequelae interfere with functioning in daily life [5].

Four genetic subgroups (WNT, SHH, Group 3 and Group 4) defined by expression patterns and epigenetic signatures allow a reliable prognostication [6]. The WHO classification (2016, [7]) developed this further to a combination of histological criteria with classic (CMB; 60-70% in adults), desmoplastic/nodular (DNMB; 25-40%), extensive nodular (MBEN; <5%) and large cell/anaplastic (LCA, 10-25%) entities and genetically defined groups. These consist of WNT-activated, SHH-activated and TP53 wildtype, SHH-activated and TP53 altered, and Non-WNT/Non-SHH (Group 3 and 4). Patients with MYC/MYCN-amplification [6,8] and p53 mutation [9] have an inferior prognosis. In adults, group 3 does not exist.

In children, the introduction of chemotherapy combined with cranio-spinal radiotherapy improved survival [10-12], however, associated with significant unwanted effects [13]. The same regimen was retrospectively evaluated in a non-randomized adult sub-cohort [14]. Radio-chemotherapy compared to radiotherapy alone improved event-free survival (EFS) (4-year EFS, 74% *v.* 47%; p=0.027) and overall survival (OS) (4-year-OS, 94% vs. 81%; p=0.035). Retrospective data and small prospective trials also suggested an impact of chemotherapy in adult patients [15-17].

NOA-07 prospectively evaluated toxicity-related treatment terminations after 4 cycles of adjuvant chemotherapy, and the toxicity profile in the first-line treatment of adult patients with medulloblastoma. Results of the active treatment period are presented here.

Material and Methods

Treatment and ethics

NOA-07 enrolled patients at 15 sites in Germany. The trial was approved by the Ethics Committee (EC) of the University of Regensburg, Germany (08-112-0058; substantial amendment of July 01, 2016). The trial was registered at ClinicalTrials.gov (NCT01614132).

All patients with age above 21 and Chang stage T1-4 and M0 or M1 as diagnosed locally at the trial sites were included. Treatment consisted of photon cranio-spinal irradiation (1.6 Gy/35.2 Gy, posterior fossa boost 1.8 Gy/55 Gy) in combination with vincristine (1.5 mg/m^2 weekly, cap at 2.0 mg), followed by a maximum of eight six-weekly cycles of cisplatin (70.0 mg/m^2, day 1), lomustine (75.0 mg/m^2, day 1) and vincristine (1.5 g/m^2, cap at 2.0 mg, days 1, 8, 15). Treatment per protocol was at least one cycle of adjuvant chemotherapy (Suppl. Figure 1).

Imaging (MRI) classification

Cranio-spinal imaging patterns (MRI with T1-weighted (w) images, T1-w post gadolinium-containing contrast agent (Gd), T2-w, FLAIR) were evaluated prospectively. Inclusion was based on the local (neuro)radiology report. All imaging was reviewed for localization, extent of resection, and progression [18].

Contrast enhancing and non-enhancing tumor volume was calculated from voxel size x^3 multiplied with the number of target voxels using the IntelliSpace Portal® (Philips Healthcare). Extent of resection was evaluated for the enhancing tumor volume on early postsurgical MRI (24 to 72 h post-operative). Tumor progression was assessed on follow-up cranio-spinal MRIs after radiotherapy, before starting adjuvant chemotherapy and in 12-weekly time intervals over three years, and six-monthly intervals thereafter.

Chang classification

Despite the fact that the Chang [3] classification was initially based on surgical reports and CT scans, and that it´s prognostic value is doubtable, patients were classified according to Chang using MRI (condensed T1-w plus gadolinium and T2-w) criteria and results from lumbar punctures, with the aim to morphologically describe the study population.

Histological and molecular classification and CSF assessment

All specimens were diagnosed locally and referenced by at least two experienced neuropathologists [19]. After introduction of 2016 WHO classification amendment [7], all specimens were re-evaluated and an integrated diagnosis was reported.

Immunohistochemistry was performed as described [20]. Genetic entities were defined using immunohistochemistry with antibodies against ß-Catenin, Yap1, p75-NGFR, Otx2 and p53. DNA was extracted, and direct sequencing (Sanger) of exon 3 of CTNNB1 was performed [21]. Genome-wide copy number estimation and analysis of allelic distribution was performed by molecular inversion profiling (MIP) [22] and analyzed by Nexus Copy Number 7.0 Discovery Edition software (BioDiscovery, El Segundo, CA, U.S.A.). If minimal DNA was available, a multiplex ligation-dependent probe amplification (MLPA) was done [23].

Global DNA methylation profiling using the Illumina Human Methylation 450 Bead Chip array was performed. Medulloblastoma subgrouping were done as described [20,24]. Genome-wide copy number profiles were generated using the ‘conumee’ package (https://www.bioconductor.org/packages/release/bioc/html/conumee.html) in the R programming environment.

As meningeosis in adults with medulloblastoma is not well described, CSF punctures were done in all patients at the time of diagnosis and recommended every 3 months thereafter or if clinical symptoms occurred. CSF was referenced centrally.

Feasibility and toxicity

Prospectively defined toxicity-related treatment terminations after 4 cycles of adjuvant chemotherapy, and the toxicity profile were primary endpoints and prospectively documented.

Adverse events (using Common Toxicity Criteria v3.0 [25]) were evaluated and graded at every visit, and causality of treatment was assessed. Dose de-escalation rules are detailed in Suppl. Table 1. Severe adverse events were handled by a safety board following international guidelines. An external data safety monitoring board supervised the trial.

An arbitrary cut-off of 45 years was used in a post-hoc analyses to compare toxicity in younger vs. older patients.

Efficacy

Event free (EFS), progression free (PFS) and overall survival (OS) at 3 and 5 years were secondary endpoints and recorded at each site visit. EFS was defined as time from study inclusion to disease progression, death, or discontinuation of treatment. PFS was a combined imaging and clinical endpoint adapted to the response assessment in neuro-oncology (RANO) criteria [26] and defined as time from study inclusion to disease progression or death. OS was calculated from study inclusion to death.

Health-related quality of life evaluation

Health-related quality of life (HRQoL) was prospectively evaluated before radio-chemotherapy, after radio-chemotherapy, and each three months thereafter using EORTC QLQ-C30 and QLQ-BN20 [27]. Role, cognitive and social functioning were defined for the primary analyses to reduce errors from multiple testing. The other scales were analyzed on an exploratory basis. A difference in the mean value of HRQoL parameters of ≥10 points was set to be 'clinically meaningful' [28].

Cognitive testing

Cognition was prospectively evaluated at baseline before radio-chemotherapy, after radio-chemotherapy, and each three months thereafter. The Controlled Oral Word Association Test (COWA [29]) was used to measure lexical verbal fluency. Semantic verbal fluency was measured by the Regensburger Wortflüssigkeitstest (RWT; [30]). Verbal working-memory was measured with the digit span forward and backward from the German version of the WAIS-R [31]. TrailMaking Tests (Parts A and B) were used to measure complex visual perceptual tracking, planning and flexibility [32]. Raw scores were transformed into adjusted z-scores, and a mean z-score was calculated, indicating group performance. Performance not reaching a z-score of -1 was described as impaired. A healthy control population matched for age, gender and education was used.

Statistical analysis

In this prospective descriptive trial, a~~A~~ total of 30 patients was considered to be the minimum population to evaluate feasibility. The incidence of treatment terminations within the first 4 cycles of chemotherapy was determined as the primary endpoint to measure feasibility [33]. Based on published data [34], ~~an incidence of more than 60% toxicity-related treatment terminations was defined as inacceptable. Subsequently, the treatment would be feasible if the upper limit of the 95%-confidence was below 60%.~~ we hypothesized that if the study population consists of 30 patients, and less than 18 patients (60%) or maximally 17 patients (56.7%) would have to terminate treatment due to toxicity, the primary endpoint would be met~~With a study population of 30 patients, the primary endpoint was therefore reached if at least 17 of 30 patients (56.7%) would receive at least four cycles of maintenance chemotherapy, or 44.3% would not be terminated before four cycles were concluded (p1)~~ (NQuery 4.0; Statistical Solutions, Boston, USA).

All primary end point data are presented descriptively. The 3 year EFS / PFS rate was estimated by using binary proportions. PFS and OS analysis was performed using the Kaplan-Meier method. Correlations between data groups were evaluated by Spearman Rank analysis. Comparative statistical analysis for rates and proportions was performed using Chi square analysis. For two group comparison, Wilcoxon rank-sum tests were computed. The significance level was defined as $p<0.05$ (Stata 14; StataCorp LP, College Station, Texas, USA).

Results

Patient characteristics

From 2009 to 2014, 33 patients were included at 15 German centers. Thirty patients were evaluable, and 25 of them (83.3%) were treated *per protocol* (Suppl. Figure 1). Median age was 37 (range, 21-53), the median Karnofsky Performance Status (KPS) at inclusion was 90 (range, 50-100), and 77.0% of patients had a KPS of 90 or above at baseline (Table 1).

Imaging (MRI) classification

Most tumors were lateral/hemispheric (Table 1), and 6.7% of patients showed signs of leptomeningeal spread (Table 1 and 2). M2 and M3 disease was only diagnosed during MRI reference evaluation. These patients were included in the study based on local evaluation.

Enhancing tumor was completely resected in 15 patients (Suppl. Table 2). After combined radio-chemotherapy, 73.3% of patients had a complete response (Suppl. Table 2). No patient progressed before starting adjuvant chemotherapy.

Chang classification

Twenty-six of 30 tumors were classifiable, showing a mixed pattern (Table 2). If evaluations were based on local readings, the incidence of M2 and M3 disease was much lower (6.7% of patients; n=2).

Histological and genetic classification and CSF evaluation

Each 50% of tumors were into the classic and desmoplastic/nodular entities (Table 1; Figure 1). Twenty-nine of 30 patients could be assigned to genetically defined entities by immunohistochemistry, and 23 of these were evaluable by 450k methylation classification [35] with congruent results (Table 1). CTNNB1 exon 3 was mutated in all 4 WNT-activated tumors (D32V, S33F, S33P, S37Y). Whole genomic copy number and allelic distribution were analyzed without evidence for amplifications of MYC, MYCN or GLI2. One SHH-activated tumor showed copy number losses 9q and chr14, typical for SHH-activated subgroups. However, 17p losses (TP53) were not found in SHH-activated cases, which is in line with the absence of TP53 accumulation (Figure 1).

Twenty-six of 30 patients (86.6%) had a lumbar puncture at diagnosis. Three patients were diagnosed with leptomeningeal spread on lumbar CSF evaluation, one of them with central review that verified the diagnosis (Table 1). Central review was performed only in the minority of cases (9/30 patients; 1 of them with discrepancy in between local and central). Lumbar punctures after diagnosis were only performed if meningeosis was suspected, and no systematic data could be raised.

Feasibility and toxicity

All patients were treated with standard photon-based radiotherapy. Radio-chemotherapy was completed in all patients (Table 3). Two patients terminated therapy before maintenance chemotherapy was started, one with tuberculosis and paralytic ileus, and one with pneumonia with sepsis. Two patients were lost because they withdrew informed

consent, and one patient changed to a local institution after radio-chemotherapy, which was not registered as study site. Seventy percent of patients (n=21) tolerated at least four cycles of chemotherapy, all of them with dose modifications. Therefore, the pre-specified feasibility goal of ~~at least 45%~~more than 60% of patients receiving at least 4 cycles of maintenance chemotherapy was met.

One patient progressed after the fifth adjuvant cycle. All other patients were discontinued due to treatment-related toxicity or withdrawal of informed consent (Table 3). Seventy-seven out of 155 cycles were given per protocol (49.7%; Table 3 and Suppl. Figure 2A and B).

Leukopenia was the major toxicity. Polyneuropathy and ototoxicity were the only grade 3 or 4 non-hematological toxicities (Table 4). Six patients had grade I, 4 patients grade 2, and 4 patients grade 3 polyneuropathy.

Events were also calculated as events per cycle and showed an increase of toxicity over treatment time (Table 4, Suppl. Table 3, and Suppl. Figure 2B). Treatment was terminated or dose intensity was reduced in almost 60% of patients at cycle 4 due to side effects (Suppl. Figure 2B). Of note, Vincristine was stopped early on in a large number of patients, whereas lumustine and cisplatin were typically stopped later in the course of treatment. The number of severe adverse events per patient was highly variable (range 0-23).

Feasibility appeared to be age-dependent. Post-hoc analyses showed that 72.7% of patients below age 45 received four cycles of chemotherapy, but only 62.5% of patients older than 45. Testing for all eight adjuvant cycles revealed that 45.5% of all patients younger than 45 years completed eight cycles, whereas only 12.5% of patients over 45 years received all cycles. Severe adverse events were significantly more frequent in patients older than 45 years of age ($p = 0.040$). We observed no treatment-related deaths.

Health-related quality of Life

Compliance to HRQoL evaluation was > 65% at most time points (Suppl. Table 4). Scoring was reduced (≥10 points) in role, cognitive and social functioning directly post-operative, where role and social functioning was also significantly worse in comparison to a glioblastoma population [36,37] (Suppl. Table 5). On a group level, role, cognitive and social functioning improved over time (Figure 2). Similar results were found for the exploratory HRQoL items (Suppl. Figure 3).

Cognition

Compliance to cognition testing was 44.5%. On a group level, scores for working memory remained within normal limits. Attention was impaired at all time points, and visual perception was impaired at the first and the second measurement, but returned to normal in the third measurement with a mean performance above z=-1. Lexical verbal fluency (Controlled Oral Word Association Test COWA, n=7, M1=-1.8, M3=-0.6, $p<0.02$) and semantic verbal fluency (food naming, n=7, M1=-1.92, M3=-0.42, $p<005$) were impaired before radio-chemotherapy, but reached an average level of z=-0.84 and z=-1.0 in the third measurement, indicating improvement to normal (Suppl. Figure 4).

Efficacy

At databank lock (June 1st, 2016), median follow-up was 58.0 months, and a total of seven patients had relapsed, amongst them one patient with M3 disease (CMB, genetic entity Non-WNT/Non-SHH; no MYC/MYCN amplification or *TP53* mutation), one patient with Non-WNT/Non-SHH M0, and five patients with SHH-activated tumors, none of them with p53 mutation or MYCN amplification. (Table 1). Three patients died in the treatment phase, all from tumor-related complications (epileptic seizure in the bathtub, aspiration pneumonia, and suicide).

The 3-year EFS rate was 66.6%, the 3 year PFS and OS rates were 66.6%. and 70.0% respectively. With 83% patients without progression and 90% of all patients still alive, median PFS and OS were not reached. Genetic subgroups were not pre-specified to be explored for efficacy due to limited patient numbers.

Correlation analysis

Only one of the Non-WNT/Non-SHH (Group 4) tumors was Chang M3 at diagnosis. Almost all tumors with a lateral localization in MRI were SHH-activated (90.9%) (p = 0.040). Non-WNT/Non-SHH-activated tumors were lateral in 20% of cases, and not a single WNT-activated tumor was lateral (p = 0.01). Both, lateral location and SHH-activation were associated with a higher proportion of complete resections (63.6% vs. 36.8%; p=0.018 and 45.3% vs. 38.7%; p=0.026). Accordingly, after volumetric evaluation of MRI, complete tumor resections were more prevalent in the SHH-activated tumors (97.5% vs. 86.9%; p=0.024).

Relapses were more prevalent in the SHH-activated tumors (80% of recurrent cases were SHH vs. 64% of non-recurrent cases; p = 0.091) (Suppl. Table 6).

Discussion

NOA-07 is a prospective descriptive trial to evaluate feasibility and toxicity of combined radio-polychemotherapy in adults with newly diagnosed medulloblastoma. The primary endpoint, the number of toxicity-related treatment terminations after 4 cycles of adjuvant chemotherapy, was justified retrospectively by upcoming data that suggest that a decreased number of treatment cycles is not decisive for progression-free or overall survival in children with average-risk medulloblastoma [38]. The regimen was feasible for at least four cycles of maintenance chemotherapy in 70.0% of patients. The pre-specified study goal ~~of at~~

~~least~~that more than 18 patients (~~45~~60% ~~of patients~~) could be treated with at least 4 cycles of chemotherapy was therefore met. Considerable and increasing toxicity was observed, with polyneuropathy as the main non-hematological toxicity occurring early within treatment, and leukopenia and thrombocytopenia as the most prevalent hematological toxicities. Sixty-seven percent of patients went off-study due to toxicity under maintenance chemotherapy. We therefore conclude that the regimen induces more severe toxicity than in comparable pediatric trials.

Recent publications suggest that Vincristine, that induces a high rate of neurotoxicity, may be fully deleted without endangering efficacy [39], and that alternative agents may possibly replace vincristine during concomitant radio-chemotherapy [40]. In addition, attenuated maintenance regimen may decrease toxicity while sustaining efficacy [41].

With adherence to strict de-escalation rules, toxicity was manageable. No unexpected severe adverse events were recorded. In a non-randomized retrospectively evaluated cohort of young adults treated with the same regimen [14], 28 of 47 patients (59.6%) received the full number of eight maintenance chemotherapy cycles. Median age was 37.0 in our trial and 28.5 years in the other cohort. This difference in age may indicate decreased feasibility in older patients. Accordingly, feasibility was age-dependent in NOA-07, with a higher rate of adverse and a significantly higher rate of severe adverse events in patients above age 45.

Long-term neurotoxicity is a major concern in radio-chemotherapy regimens involving the brain [5,42,43]. In a Canadian trial that focused on medulloblastoma patients in their second life decade, long-term ototoxicity and neurotoxicity of CTC grade 2 or above occurred in 45.0% and 71.0% of patients [5]. Long-term toxicity results of NOA-07 are lacking due to the short follow-up time of 58.0 months in median and will be reported after all patients have been followed for 5 years.

HRQoL and cognition are important correlates of toxicity and long-term outcomes. During the active treatment phase of NOA-07, HRQoL and cognitive function improved.

Long-term data will be supplemented by a social outcome analysis that will mainly focus on long-term social function.

Study results from Packer and co-workers indicate that radiotherapy plus concomitant and adjuvant chemotherapy is superior to radiotherapy alone in children [10,12,44]. Patients in the Friedrich trial [14] experienced a 4-year event-free survival rate (EFS) of 68.0% and a 4-year overall survival (OS) rate of 89.0%, similar to premature data in NOA-07. A recent meta-analysis by Kocakaya et al. showed that patients receiving chemotherapy first-line survived significantly longer (mOS: 108 mo, 95.0% CI: 68.6-148.0) than patients treated with radiotherapy alone (mOS: 57 mo, 95.0% CI: 39.6-74.4) [45]. Importantly, published data also show that the risk of recurrence appears to increase markedly with time [17]. In conclusion, published evidence strongly indicates a role for combined radio-chemotherapy for adults with medulloblastoma, but also warrants long-term follow up in this population. The NOA-07 protocol ~~, however,~~ is the first trial that evaluated these questions prospectively.

We further analyzed MR imaging, histological and molecular patterns to detect unusual patterns on a descriptive and correlative level. Our results correspond well to published results [4,6,20,24,46]. Of note, metastatic disease (Chang M1 to M3) was found in one third of patients during central review, but only 6.7% in local evaluations. This points to a strict central review strategy during diagnostic workup, as metastatic disease is connected to worse outcomes [3] and may mandate adapted treatment strategies.

Reference analysis of medulloblastoma subgroups showed the expected histological and genetic distribution. The genetic pattern in WNT-activated adult patients in our dataset was different from children and might indicate a different biology and explain the worse prognosis [444]. The SHH-subgroup is highly overrepresented in adults, and SHH-activated tumors had a favorable outcome in infants and young children (5-year OS 77.0%), compared to older children (5-year OS 68.0%) and adults (5-year OS 34.0%) [664]. In NOA-07, 5 of 7 early relapses were SHH-activated. All SHH-activated tumors in our series represented the

SHH-activated TP53 wildtype entity, none showed *MYC/MYCN*-amplification, and the subgroup comprised a higher rate of complete resections and comparable dose intensities during radio-chemotherapy.

Shortcomings of this trial are limited patient numbers, the distribution of patients to a large number of centers that may increase toxicity rates due to lower experience of the involved investigators, and the non-randomized design. However, the trial was powered for feasibility and toxicity as its primary endpoint.

In summary, this prospective descriptive trial evaluated feasibility and toxicity of a radio-polychemotherapy regimen in a homogenous cohort of intermediate prognostic adults with medulloblastoma, as well as imaging, histological and molecular parameters, HRQoL, cognition, and EFS, PFS and OS outcomes. Long-term evaluations are ongoing. We conclude that combined radio-chemotherapy is associated with considerable toxicity and mandates pre-defined tapering rules and dose modifications in the majority of patients. Modified regimen may increase feasibility of radio-polychemotherapy of adult patients with medulloblastoma.

Acknowledgements:

This work is dedicated to our esteemed colleague, Joachim Kühl, MD, deceased, who was one of the driving forces to initiate this trial. We cordially thank all investigators and study staff in the centers who did a tremendous job to compile all data.

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Figure legends

Figure 1

Histological and genetic distribution in NOA-07. Figure A: Clustering of samples based on the 5.000 most differentially methylated CpG probes (standard deviation), with DNA methylation values shown from unmethylated (blue) to methylated (red). SHH-activated, WNT-activated and Non-WNT/Non-SHH (Group 4) tumors are clearly distinct. DNMB, desmoplastic nodular medulloblastoma; CMB classic medulloblastoma. Figure 1B: Summary of copy number profiles per molecular subgroup. Log2 copy number ratios (tumor : normal) are displayed on a scale from loss (red) to gain (green). Notable changes include monosomy 6 in one WNT-activated sample, loss of 9q in a subset of SHH-activated tumors, and iso(17q) in all three Non-WNT/Non-SHH (Group 4) tumors.

Figure 2

Health-related quality of life (HRQoL) evaluation (main categories). Scores over time for the three preselected scales (role functioning, Figure 2A; cognitive functioning, Figure 2B; and social functioning, Figure 2C), with the number of patients with HRQoL data at each time point.

Table legends

Table 1

Baseline patient characteristics. Age, gender, KPS, cranial and spinal MR imaging patterns, lumbar punctures (cerebrospinal fluid, CSF), histological and molecular subtype were recorded.

Table 2

Modified Chang classification [333] evaluated from imaging and CSF patterns. Condensed contrast-enhanced T1-w post Gd and T2-w imaging, lumbar puncture results and additional staging were included. T stands for primary tumor, M for metastasis. T1 is tumor less than 3 cm in diameter and limited to midline, roof of the fourth ventricle, and cerebellar hemispheres. T2 is tumor more than 3 cm in diameter, invading one adjacent structures or partially filling the fourth ventricle. T4 is tumor spreading through the aqueduct of Sylvius, or tumor extending to the upper cervical cord. M0 stands for no evidence of metastasis. M1 is microscopic tumor cells in the cerebrospinal fluid, M2 is gross nodular seedings demonstrated in the subarachnoid space, or ventricles. M3 is gross nodular seeding in the spinal subarachnoid space, and M4 is extra-neural metastasis. * indicates missing data due to lacking source imaging data.

Table 3

Treatment compliance and duration. Time to start of each treatment part was calculated from time of tumor resection to first day of the respective treatment. Extent of resection was calculated from post-operative MRI, and compliance to radio-chemotherapy and maintenance chemotherapy was extracted.

Table 4

Hematological and non-hematological toxicity Grade 1 & 2 and 3 & 4 according to CTC version 3.0. Toxicity was evaluated during radio-chemotherapy and during maintenance chemotherapy. Percentages were calculated in relation to patients under treatment at the respective time point.

N-O-D-17-00180R1

Multicenter pilot study of radio-chemotherapy as first-line treatment for adults with medulloblastoma (NOA-07)

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Running title:

Radio-chemotherapy for adults with medulloblastoma

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Funding:

This work was supported by internal grants of the German Neurooncology Society (NOA); and an unrestricted educational grant from medac GmbH.

The sponsors had no influence on study design, in the collection, analysis, and interpretation of data, in the writing of the report and in the decision to submit the paper for publication. The corresponding author had full access to all the data in the study and had full responsibility for the decision to submit for publication.

Conflict of interest:

None related to the work presented here.

Total manuscript word count:

5430.

Abstract

Background: Medulloblastoma in adult patients is rare, with 0.6 cases per million. Prognosis depends on clinical factors and medulloblastoma entity. No prospective data on the feasibility of radio-chemotherapy exist. The German Neuro-Oncology Working Group (NOA) performed a prospective descriptive multicenter single-arm Phase II trial to evaluate feasibility and toxicity of radio-polychemotherapy.

Methods: The NOA-07 trial combined cranio-spinal irradiation with vincristine, followed by eight cycles of cisplatin, lomustine and vincristine. Adverse events, imaging and progression patterns, histological and genetic markers, health-related quality of life (HRQoL) and cognition were evaluated. Primary endpoint was the rate of toxicity-related treatment terminations after four chemotherapy cycles, and the toxicity profile. The feasibility goal was reached if at least 45% of patients received at least 4 cycles of maintenance chemotherapy.

Results: Thirty patients were evaluable. Each 50% percent showed classic and desmoplastic-nodular histology. Sixty-seven percent were classified into the sonic hedgehog (SHH) subgroup without *TP53* alterations, 13% in wingless (WNT), and 17% in Non-WNT/Non-SHH. Four cycles of chemotherapy were feasible in the majority (n=21; 70.0%). Hematological side effects and polyneuropathy were prevalent toxicities. During the active treatment period, HRQoL and verbal fluency improved significantly. The 3-year event-free survival rate (EFS) was 66.6% at the time of databank lock.

Conclusions: Radio-polychemotherapy did lead to considerable toxicity and a high amount of dose reductions throughout the first four chemotherapy cycles that may affect efficacy. Thus, we propose frequent patient surveillance using this regimen. Modifications of the regimen may increase feasibility of radio-polychemotherapy of adult patients with medulloblastoma.

Key words:

Medulloblastoma, radio-chemotherapy, health-related quality of life, cognition, imaging

Importance of the study:

NOA-07 showed that combined radio-chemotherapy followed by maintenance chemotherapy with cisplatin, lomustine, and vincristine is more toxic in adults than in children. This prospective descriptive trial constitutes a unique dataset that perpetuates the development of effective treatments in this curable population. The results have potential to influence or even change clinical practice. The NOA-07 protocol can be translated to the recommendation that adults with medulloblastoma should be treated with attenuated radio-polychemotherapy regimen that consider the decreased feasibility of radio-polychemotherapy in adults in comparison to children. In addition, an attenuated NOA-07 regimen may serve as a basis for the standard arm in a subsequent trial. Current knowledge makes it likely that such a trial will ask a molecular question in its experimental arm and will lead into a molecularly stratified approach for adults with medulloblastoma.

Introduction

Medulloblastoma is rare in adults. About 70% of cases occur in patients younger than 15 years [1]. The US SEER database reports 0.6 cases per million in adults per year [2]. Five-year overall survival depends on clinical prognostic factors [3], and on histological entity and genetic subgroup [4], and reaches 40-90%. Long-term sequelae interfere with functioning in daily life [5].

Four genetic subgroups (WNT, SHH, Group 3 and Group 4) defined by expression patterns and epigenetic signatures allow a reliable prognostication [6]. The WHO classification (2016, [7]) developed this further to a combination of histological criteria with classic (CMB; 60-70% in adults), desmoplastic/nodular (DNMB; 25-40%), extensive nodular (MBEN; <5%) and large cell/anaplastic (LCA, 10-25%) entities and genetically defined groups. These consist of WNT-activated, SHH-activated and TP53 wildtype, SHH-activated and TP53 altered, and Non-WNT/Non-SHH (Group 3 and 4). Patients with MYC/MYCN-amplification [6,8] and p53 mutation [9] have an inferior prognosis. In adults, group 3 does not exist.

In children, the introduction of chemotherapy combined with cranio-spinal radiotherapy improved survival [10-12], however, associated with significant unwanted effects [13]. The same regimen was retrospectively evaluated in a non-randomized adult sub-cohort [14]. Radio-chemotherapy compared to radiotherapy alone improved event-free survival (EFS) (4-year EFS, 74% *v.* 47%; p=0.027) and overall survival (OS) (4-year-OS, 94% vs. 81%; p=0.035). Retrospective data and small prospective trials also suggested an impact of chemotherapy in adult patients [15-17].

NOA-07 prospectively evaluated toxicity-related treatment terminations after 4 cycles of adjuvant chemotherapy, and the toxicity profile in the first-line treatment of adult patients with medulloblastoma. Results of the active treatment period are presented here.

Material and Methods

Treatment and ethics

NOA-07 enrolled patients at 15 sites in Germany. The trial was approved by the Ethics Committee (EC) of the University of Regensburg, Germany (08-112-0058; substantial amendment of July 01, 2016). The trial was registered at ClinicalTrials.gov (NCT01614132).

All patients with age above 21 and Chang stage T1-4 and M0 or M1 as diagnosed locally at the trial sites were included. Treatment consisted of photon cranio-spinal irradiation (1.6 Gy/35.2 Gy, posterior fossa boost 1.8 Gy/55 Gy) in combination with vincristine (1.5 mg/m^2 weekly, cap at 2.0 mg), followed by a maximum of eight six-weekly cycles of cisplatin (70.0 mg/m^2, day 1), lomustine (75.0 mg/m^2, day 1) and vincristine (1.5 g/m^2, cap at 2.0 mg, days 1, 8, 15). Treatment per protocol was at least one cycle of adjuvant chemotherapy (Suppl. Figure 1).

Imaging (MRI) classification

Cranio-spinal imaging patterns (MRI with T1-weighted (w) images, T1-w post gadolinium-containing contrast agent (Gd), T2-w, FLAIR) were evaluated prospectively. Inclusion was based on the local (neuro)radiology report. All imaging was reviewed for localization, extent of resection, and progression [18].

Contrast enhancing and non-enhancing tumor volume was calculated from voxel size x^3 multiplied with the number of target voxels using the IntelliSpace Portal® (Philips Healthcare). Extent of resection was evaluated for the enhancing tumor volume on early postsurgical MRI (24 to 72 h post-operative). Tumor progression was assessed on follow-up cranio-spinal MRIs after radiotherapy, before starting adjuvant chemotherapy and in 12-weekly time intervals over three years, and six-monthly intervals thereafter.

Chang classification

Despite the fact that the Chang [3] classification was initially based on surgical reports and CT scans, and that it´s prognostic value is doubtable, patients were classified according to Chang using MRI (condensed T1-w plus gadolinium and T2-w) criteria and results from lumbar punctures, with the aim to morphologically describe the study population.

Histological and molecular classification and CSF assessment

All specimens were diagnosed locally and referenced by at least two experienced neuropathologists [19]. After introduction of 2016 WHO classification amendment [7], all specimens were re-evaluated and an integrated diagnosis was reported.

Immunohistochemistry was performed as described [20]. Genetic entities were defined using immunohistochemistry with antibodies against ß-Catenin, Yap1, p75-NGFR, Otx2 and p53. DNA was extracted, and direct sequencing (Sanger) of exon 3 of CTNNB1 was performed [21]. Genome-wide copy number estimation and analysis of allelic distribution was performed by molecular inversion profiling (MIP) [22] and analyzed by Nexus Copy Number 7.0 Discovery Edition software (BioDiscovery, El Segundo, CA, U.S.A.). If minimal DNA was available, a multiplex ligation-dependent probe amplification (MLPA) was done [23].

Global DNA methylation profiling using the Illumina Human Methylation 450 Bead Chip array was performed. Medulloblastoma subgrouping were done as described [20,24]. Genome-wide copy number profiles were generated using the ‘conumee’ package (https://www.bioconductor.org/packages/release/bioc/html/conumee.html) in the R programming environment.

As meningeosis in adults with medulloblastoma is not well described, CSF punctures were done in all patients at the time of diagnosis and recommended every 3 months thereafter or if clinical symptoms occurred. CSF was referenced centrally.

Feasibility and toxicity

Prospectively defined toxicity-related treatment terminations after 4 cycles of adjuvant chemotherapy, and the toxicity profile were primary endpoints and prospectively documented.

Adverse events (using Common Toxicity Criteria v3.0 [25]) were evaluated and graded at every visit, and causality of treatment was assessed. Dose de-escalation rules are detailed in Suppl. Table 1. Severe adverse events were handled by a safety board following international guidelines. An external data safety monitoring board supervised the trial.

An arbitrary cut-off of 45 years was used in a post-hoc analyses to compare toxicity in younger vs. older patients.

Efficacy

Event free (EFS), progression free (PFS) and overall survival (OS) at 3 and 5 years were secondary endpoints and recorded at each site visit. EFS was defined as time from study inclusion to disease progression, death, or discontinuation of treatment. PFS was a combined imaging and clinical endpoint adapted to the response assessment in neuro-oncology (RANO) criteria [26] and defined as time from study inclusion to disease progression or death. OS was calculated from study inclusion to death.

Health-related quality of life evaluation

Health-related quality of life (HRQoL) was prospectively evaluated before radio-chemotherapy, after radio-chemotherapy, and each three months thereafter using EORTC QLQ-C30 and QLQ-BN20 [27]. Role, cognitive and social functioning were defined for the primary analyses to reduce errors from multiple testing. The other scales were analyzed on an exploratory basis. A difference in the mean value of HRQoL parameters of ≥10 points was set to be 'clinically meaningful' [28].

Cognitive testing

Cognition was prospectively evaluated at baseline before radio-chemotherapy, after radio-chemotherapy, and each three months thereafter. The Controlled Oral Word Association Test (COWA [29]) was used to measure lexical verbal fluency. Semantic verbal fluency was measured by the Regensburger Wortflüssigkeitstest (RWT; [30]). Verbal working-memory was measured with the digit span forward and backward from the German version of the WAIS-R [31]. TrailMaking Tests (Parts A and B) were used to measure complex visual perceptual tracking, planning and flexibility [32]. Raw scores were transformed into adjusted z-scores, and a mean z-score was calculated, indicating group performance. Performance not reaching a z-score of -1 was described as impaired. A healthy control population matched for age, gender and education was used.

Statistical analysis

In this prospective descriptive trial, a total of 30 patients was considered to be the minimum population to evaluate feasibility. The incidence of treatment terminations within the first 4 cycles of chemotherapy was determined as the primary endpoint to measure feasibility [33]. Based on published data [34], we hypothesized that if the study population consists of 30 patients, and less than 18 patients (60%) or maximally 17 patients (56.7%) would have to terminate treatment due to toxicity, the primary endpoint would be met (NQuery 4.0; Statistical Solutions, Boston, USA).

All primary end point data are presented descriptively. The 3 year EFS / PFS rate was estimated by using binary proportions. PFS and OS analysis was performed using the Kaplan-Meier method. Correlations between data groups were evaluated by Spearman Rank analysis. Comparative statistical analysis for rates and proportions was performed using Chi square analysis. For two group comparison, Wilcoxon rank-sum tests were computed. The

significance level was defined as $p<0.05$ (Stata 14; StataCorp LP, College Station, Texas, USA).

Results

Patient characteristics

From 2009 to 2014, 33 patients were included at 15 German centers. Thirty patients were evaluable, and 25 of them (83.3%) were treated *per protocol* (Suppl. Figure 1). Median age was 37 (range, 21-53), the median Karnofsky Performance Status (KPS) at inclusion was 90 (range, 50-100), and 77.0% of patients had a KPS of 90 or above at baseline (Table 1).

Imaging (MRI) classification

Most tumors were lateral/hemispheric (Table 1), and 6.7% of patients showed signs of leptomeningeal spread (Table 1 and 2). M2 and M3 disease was only diagnosed during MRI reference evaluation. These patients were included in the study based on local evaluation.

Enhancing tumor was completely resected in 15 patients (Suppl. Table 2). After combined radio-chemotherapy, 73.3% of patients had a complete response (Suppl. Table 2). No patient progressed before starting adjuvant chemotherapy.

Chang classification

Twenty-six of 30 tumors were classifiable, showing a mixed pattern (Table 2). If evaluations were based on local readings, the incidence of M2 and M3 disease was much lower (6.7% of patients; n=2).

Histological and genetic classification and CSF evaluation

Each 50% of tumors were into the classic and desmoplastic/nodular entities (Table 1;

Figure 1). Twenty-nine of 30 patients could be assigned to genetically defined entities by immunohistochemistry, and 23 of these were evaluable by 450k methylation classification [35] with congruent results (Table 1). CTNNB1 exon 3 was mutated in all 4 WNT-activated tumors (D32V, S33F, S33P, S37Y). Whole genomic copy number and allelic distribution were analyzed without evidence for amplifications of MYC, MYCN or GLI2. One SHH-activated tumor showed copy number losses 9q and chr14, typical for SHH-activated subgroups. However, 17p losses (TP53) were not found in SHH-activated cases, which is in line with the absence of TP53 accumulation (Figure 1).

Twenty-six of 30 patients (86.6%) had a lumbar puncture at diagnosis. Three patients were diagnosed with leptomeningeal spread on lumbar CSF evaluation, one of them with central review that verified the diagnosis (Table 1). Central review was performed only in the minority of cases (9/30 patients; 1 of them with discrepancy in between local and central). Lumbar punctures after diagnosis were only performed if meningeosis was suspected, and no systematic data could be raised.

Feasibility and toxicity

All patients were treated with standard photon-based radiotherapy. Radio-chemotherapy was completed in all patients (Table 3). Two patients terminated therapy before maintenance chemotherapy was started, one with tuberculosis and paralytic ileus, and one with pneumonia with sepsis. Two patients were lost because they withdrew informed consent, and one patient changed to a local institution after radio-chemotherapy, which was not registered as study site. Seventy percent of patients (n=21) tolerated at least four cycles of chemotherapy, all of them with dose modifications. Therefore, the pre-specified feasibility goal of more than 60% of patients receiving at least 4 cycles of maintenance chemotherapy was met.

One patient progressed after the fifth adjuvant cycle. All other patients were discontinued due to treatment-related toxicity or withdrawal of informed consent (Table 3). Seventy-seven out of 155 cycles were given per protocol (49.7%; Table 3 and Suppl. Figure 2A and B).

Leukopenia was the major toxicity. Polyneuropathy and ototoxicity were the only grade 3 or 4 non-hematological toxicities (Table 4). Six patients had grade I, 4 patients grade 2, and 4 patients grade 3 polyneuropathy.

Events were also calculated as events per cycle and showed an increase of toxicity over treatment time (Table 4, Suppl. Table 3, and Suppl. Figure 2B). Treatment was terminated or dose intensity was reduced in almost 60% of patients at cycle 4 due to side effects (Suppl. Figure 2B). Of note, Vincristine was stopped early on in a large number of patients, whereas lumustine and cisplatin were typically stopped later in the course of treatment. The number of severe adverse events per patient was highly variable (range 0-23).

Feasibility appeared to be age-dependent. Post-hoc analyses showed that 72.7% of patients below age 45 received four cycles of chemotherapy, but only 62.5% of patients older than 45. Testing for all eight adjuvant cycles revealed that 45.5% of all patients younger than 45 years completed eight cycles, whereas only 12.5% of patients over 45 years received all cycles. Severe adverse events were significantly more frequent in patients older than 45 years of age ($p = 0.040$). We observed no treatment-related deaths.

Health-related quality of Life

Compliance to HRQoL evaluation was > 65% at most time points (Suppl. Table 4). Scoring was reduced (≥10 points) in role, cognitive and social functioning directly post-operative, where role and social functioning was also significantly worse in comparison to a glioblastoma population [36,37] (Suppl. Table 5). On a group level, role, cognitive and social

functioning improved over time (Figure 2). Similar results were found for the exploratory HRQoL items (Suppl. Figure 3).

Cognition

Compliance to cognition testing was 44.5%. On a group level, scores for working memory remained within normal limits. Attention was impaired at all time points, and visual perception was impaired at the first and the second measurement, but returned to normal in the third measurement with a mean performance above z=-1. Lexical verbal fluency (Controlled Oral Word Association Test COWA, n=7, M1=-1.8, M3=-0.6, $p<0.02$) and semantic verbal fluency (food naming, n=7, M1=-1.92, M3=-0.42, $p<005$) were impaired before radio-chemotherapy, but reached an average level of z=-0.84 and z=-1.0 in the third measurement, indicating improvement to normal (Suppl. Figure 4).

Efficacy

At databank lock (June 1st, 2016), median follow-up was 58.0 months, and a total of seven patients had relapsed, amongst them one patient with M3 disease (CMB, genetic entity Non-WNT/Non-SHH; no MYC/MYCN amplification or *TP53* mutation), one patient with Non-WNT/Non-SHH M0, and five patients with SHH-activated tumors, none of them with p53 mutation or MYCN amplification. (Table 1). Three patients died in the treatment phase, all from tumor-related complications (epileptic seizure in the bathtub, aspiration pneumonia, and suicide).

The 3-year EFS rate was 66.6%, the 3 year PFS and OS rates were 66.6%. and 70.0% respectively. With 83% patients without progression and 90% of all patients still alive, median PFS and OS were not reached. Genetic subgroups were not pre-specified to be explored for efficacy due to limited patient numbers.

Correlation analysis

Only one of the Non-WNT/Non-SHH (Group 4) tumors was Chang M3 at diagnosis. Almost all tumors with a lateral localization in MRI were SHH-activated (90.9%) (p = 0.040). Non-WNT/Non-SHH-activated tumors were lateral in 20% of cases, and not a single WNT-activated tumor was lateral (p = 0.01). Both, lateral location and SHH-activation were associated with a higher proportion of complete resections (63.6% vs. 36.8%; p=0.018 and 45.3% vs. 38.7%; p=0.026). Accordingly, after volumetric evaluation of MRI, complete tumor resections were more prevalent in the SHH-activated tumors (97.5% vs. 86.9%; p=0.024).

Relapses were more prevalent in the SHH-activated tumors (80% of recurrent cases were SHH vs. 64% of non-recurrent cases; p = 0.091) (Suppl. Table 6).

Discussion

NOA-07 is a prospective descriptive trial to evaluate feasibility and toxicity of combined radio-polychemotherapy in adults with newly diagnosed medulloblastoma. The primary endpoint, the number of toxicity-related treatment terminations after 4 cycles of adjuvant chemotherapy, was justified retrospectively by upcoming data that suggest that a decreased number of treatment cycles is not decisive for progression-free or overall survival in children with average-risk medulloblastoma [38]. The regimen was feasible for at least four cycles of maintenance chemotherapy in 70.0% of patients. The pre-specified study goal that more than 18 patients (60%) could be treated with at least 4 cycles of chemotherapy was therefore met. Considerable and increasing toxicity was observed, with polyneuropathy as the main non-hematological toxicity occurring early within treatment, and leukopenia and thrombocytopenia as the most prevalent hematological toxicities. Sixty-seven percent of

patients went off-study due to toxicity under maintenance chemotherapy. We therefore conclude that the regimen induces more severe toxicity than in comparable pediatric trials.

Recent publications suggest that Vincristine, that induces a high rate of neurotoxicity, may be fully deleted without endangering efficacy [39], and that alternative agents may possibly replace vincristine during concomitant radio-chemotherapy [40]. In addition, attenuated maintenance regimen may decrease toxicity while sustaining efficacy [41].

With adherence to strict de-escalation rules, toxicity was manageable. No unexpected severe adverse events were recorded. In a non-randomized retrospectively evaluated cohort of young adults treated with the same regimen [14], 28 of 47 patients (59.6%) received the full number of eight maintenance chemotherapy cycles. Median age was 37.0 in our trial and 28.5 years in the other cohort. This difference in age may indicate decreased feasibility in older patients. Accordingly, feasibility was age-dependent in NOA-07, with a higher rate of adverse and a significantly higher rate of severe adverse events in patients above age 45.

Long-term neurotoxicity is a major concern in radio-chemotherapy regimens involving the brain [5,42,43]. In a Canadian trial that focused on medulloblastoma patients in their second life decade, long-term ototoxicity and neurotoxicity of CTC grade 2 or above occurred in 45.0% and 71.0% of patients [5]. Long-term toxicity results of NOA-07 are lacking due to the short follow-up time of 58.0 months in median and will be reported after all patients have been followed for 5 years.

HRQoL and cognition are important correlates of toxicity and long-term outcomes. During the active treatment phase of NOA-07, HRQoL and cognitive function improved. Long-term data will be supplemented by a social outcome analysis that will mainly focus on long-term social function.

Study results from Packer and co-workers indicate that radiotherapy plus concomitant and adjuvant chemotherapy is superior to radiotherapy alone in children [10,12,44]. Patients in the Friedrich trial [14] experienced a 4-year event-free survival rate (EFS) of 68.0% and a 4-year

overall survival (OS) rate of 89.0%, similar to premature data in NOA-07. A recent meta-analysis by Kocakaya et al. showed that patients receiving chemotherapy first-line survived significantly longer (mOS: 108 mo, 95.0% CI: 68.6-148.0) than patients treated with radiotherapy alone (mOS: 57 mo, 95.0% CI: 39.6-74.4) [45]. Importantly, published data also show that the risk of recurrence appears to increase markedly with time [17]. In conclusion, published evidence strongly indicates a role for combined radio-chemotherapy for adults with medulloblastoma, but also warrants long-term follow up in this population. The NOA-07 protocol is the first trial that evaluated these questions prospectively.

We further analyzed MR imaging, histological and molecular patterns to detect unusual patterns on a descriptive and correlative level. Our results correspond well to published results [4,6,20,24,46]. Of note, metastatic disease (Chang M1 to M3) was found in one third of patients during central review, but only 6.7% in local evaluations. This points to a strict central review strategy during diagnostic workup, as metastatic disease is connected to worse outcomes [3] and may mandate adapted treatment strategies.

Reference analysis of medulloblastoma subgroups showed the expected histological and genetic distribution. The genetic pattern in WNT-activated adult patients in our dataset was different from children and might indicate a different biology and explain the worse prognosis [444]. The SHH-subgroup is highly overrepresented in adults, and SHH-activated tumors had a favorable outcome in infants and young children (5-year OS 77.0%), compared to older children (5-year OS 68.0%) and adults (5-year OS 34.0%) [664]. In NOA-07, 5 of 7 early relapses were SHH-activated. All SHH-activated tumors in our series represented the SHH-activated TP53 wildtype entity, none showed *MYC/MYCN*-amplification, and the subgroup comprised a higher rate of complete resections and comparable dose intensities during radio-chemotherapy.

Shortcomings of this trial are limited patient numbers, the distribution of patients to a large number of centers that may increase toxicity rates due to lower experience of the

involved investigators, and the non-randomized design. However, the trial was powered for feasibility and toxicity as its primary endpoint.

In summary, this prospective descriptive trial evaluated feasibility and toxicity of a radio-polychemotherapy regimen in a homogenous cohort of intermediate prognostic adults with medulloblastoma, as well as imaging, histological and molecular parameters, HRQoL, cognition, and EFS, PFS and OS outcomes. Long-term evaluations are ongoing. We conclude that combined radio-chemotherapy is associated with considerable toxicity and mandates pre-defined tapering rules and dose modifications in the majority of patients. Modified regimen may increase feasibility of radio-polychemotherapy of adult patients with medulloblastoma.

Acknowledgements:

This work is dedicated to our esteemed colleague, Joachim Kühl, MD, deceased, who was one of the driving forces to initiate this trial. We cordially thank all investigators and study staff in the centers who did a tremendous job to compile all data.

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Figure legends

Figure 1

Histological and genetic distribution in NOA-07. Figure A: Clustering of samples based on the 5.000 most differentially methylated CpG probes (standard deviation), with DNA methylation values shown from unmethylated (blue) to methylated (red). SHH-activated, WNT-activated and Non-WNT/Non-SHH (Group 4) tumors are clearly distinct. DNMB, desmoplastic nodular medulloblastoma; CMB classic medulloblastoma. Figure 1B: Summary of copy number profiles per molecular subgroup. Log2 copy number ratios (tumor : normal) are displayed on a scale from loss (red) to gain (green). Notable changes include monosomy 6 in one WNT-activated sample, loss of 9q in a subset of SHH-activated tumors, and iso(17q) in all three Non-WNT/Non-SHH (Group 4) tumors.

Figure 2

Health-related quality of life (HRQoL) evaluation (main categories). Scores over time for the three preselected scales (role functioning, Figure 2A; cognitive functioning, Figure 2B; and social functioning, Figure 2C), with the number of patients with HRQoL data at each time point.

Table legends

Table 1

Baseline patient characteristics. Age, gender, KPS, cranial and spinal MR imaging patterns, lumbar punctures (cerebrospinal fluid, CSF), histological and molecular subtype were recorded.

Table 2

Modified Chang classification [333] evaluated from imaging and CSF patterns. Condensed contrast-enhanced T1-w post Gd and T2-w imaging, lumbar puncture results and additional staging were included. T stands for primary tumor, M for metastasis. T1 is tumor less than 3 cm in diameter and limited to midline, roof of the fourth ventricle, and cerebellar hemispheres. T2 is tumor more than 3 cm in diameter, invading one adjacent structures or partially filling the fourth ventricle. T4 is tumor spreading through the aqueduct of Sylvius, or tumor extending to the upper cervical cord. M0 stands for no evidence of metastasis. M1 is microscopic tumor cells in the cerebrospinal fluid, M2 is gross nodular seedings demonstrated in the subarachnoid space, or ventricles. M3 is gross nodular seeding in the spinal subarachnoid space, and M4 is extra-neural metastasis. * indicates missing data due to lacking source imaging data.

Table 3

Treatment compliance and duration. Time to start of each treatment part was calculated from time of tumor resection to first day of the respective treatment. Extent of resection was calculated from post-operative MRI, and compliance to radio-chemotherapy and maintenance chemotherapy was extracted.

Table 4

Hematological and non-hematological toxicity Grade 1 & 2 and 3 & 4 according to CTC version 3.0. Toxicity was evaluated during radio-chemotherapy and during maintenance chemotherapy. Percentages were calculated in relation to patients under treatment at the respective time point.

Table 1

Baseline patient characteristics. Age, gender, KPS, cranial and spinal MR imaging patterns, lumbar punctures (cerebrospinal fluid, CSF), histological and molecular subtype were recorded.

Characteristic	**mean± SD** **range / n / percent of total**
Age at diagnosis	37.2 ±10 years range: 21.7-53.7 years
Gender	
Male	19 (63.3%)
Female	11 (36.7%)
KPS (at inclusion)	
100	8 (26.7%)
90	15 (50.0%)
80	2 (6.7%)
70	3 (10.0%)
60	1 (3.3%)
50	1 (3.3%)
40-0	0 (0.0%)
Localization	

Lateral/Hemispheric	11 (36.7%)
Midline	8 (26.7%)
With involvement of cerebellar peduncle	6 (20.0%)
Midline and peduncular	1 (3.3%)
Not available	4 (13.3%)
Leptomeningeal spread in MRI	9 (30.0%)
Leptomeningeal spread in lumbar puncture	3 (10.0%)
Histological entity (n=30)	
Classic	15 (50%)
Desmoplastic-nodular	15 (50%)
Anaplastic	0 (0%)
Other	0 (0%)
Genetic entity (n=29)	
SHH	20 (66.7%)
WNT	4 (13.3%)
Group 4	5 (16.7%)
Not available	1 (3.3%)

Table 2

Modified Chang classification [3] evaluated from imaging and CSF patterns. Condensed contrast-enhanced T1-w post Gd and T2-w imaging, lumbar puncture results and additional staging were included. T stands for primary tumor, M for metastasis. T1 is tumor less than 3 cm in diameter and limited to midline, roof of the fourth ventricle, and cerebellar hemispheres. T2 is tumor more than 3 cm in diameter, invading one adjacent structures or partially filling the fourth ventricle. T4 is tumor spreading through the aqueduct of Sylvius, or tumor extending to the upper cervical cord. M0 stands for no evidence of metastasis. M1 is microscopic tumor cells in the cerebrospinal fluid, M2 is gross nodular seedings demonstrated in the subarachnoid space, or ventricles. M3 is gross nodular seeding in the spinal subarachnoid space, and M4 is extra-neural metastasis. * indicates missing data due to lacking source imaging data.

	T1 (n)	**T2 (n)**	**T3a (n)**	**T3b (n)**	**T4 (n)**	**Total (n/%)**
M0 (n)	2	3	8	1	1	15 (50.0%)
M1 (n)	0	0	0	0	0	0 (0%)
M2 (n)	0	0	8	0	1	9 (30.0%)
M3 (n)	0	0	1	0	0	1 (3.3%)
M4 (n)	0	0	0	0	0	0 (0%)
Total (n/%)	2 (6.7%)	3 (10.0%)	17 (56.7%)	1 (3.3)%	2 (6.6%)	26 (86.7%)*

Table 3

Treatment compliance and duration. Time to start of each treatment part was calculated from time of tumor resection to first day of the respective treatment. Extent of resection was calculated from post-operative MRI, and compliance to radio-chemotherapy and maintenance chemotherapy was extracted. Data were calculated in the "intent to treat population".

Characteristic	n / percent of total days mean± SD
Resection	
Interval from diagnosis to resection	10 ± 15.2
Resection compliance	30 (100%)
Grade of resection	
Complete	15 (50.0%)
Partial	8 (26.7%)
Biopsy	0 (0.0%)
Data not available	7 (23.3%)
Average percentage of resection (in MRI)	94.7% ± 12.4%
Radio-chemotherapy	**Number of patients (median days; % of total)**

Interval from resection to radio-chemotherapy	53.0 ± 24
Interval from radio-chemotherapy to adjuvant chemotherapy	48.0 ± 79
Radiotherapy *per protocol*	30 (100 %)
Concomitant chemotherapy	
Less than 4 doses of VCR	2 (6.6%)
4-6 doses of VCR	16 (53.3%)
7-8 doses of VCR	12 (40.0%)
Maintenance chemotherapy	**Number of patients (% of total)**
Interval from resection to adjuvant chemotherapy	166 ± 76.5
Drop-out rate	
by cycle 1	5 (16.7%)
by cycle 2	5 (16.7%)
by cycle 3	9 (30.0%)
by cycle 4	9 (30.0%)
by cycle 5	9 (30.0%)
by cycle 6	11 (36.7%)
by cycle 7	17 (56.7%)
by cycle 8	20 (66.7%)

Cycles of chemotherapy given	155 (100%)
Cycles given *per protocol*	77 (49.7%)

Table 4

Hematological and non-hematological toxicity Grade 1 & 2 and 3 & 4 according to CTC version 3.0. Toxicity was evaluated during radio-chemotherapy and during maintenance chemotherapy. Percentages were calculated in relation to patients under treatment at the respective time point.

Toxicity type	Radio-Chemotherapy (% of affected patients)	Radio-Chemotherapy (no. of events)	Adjuvant chemotherapy (% of affected patients)	Adjuvant chemotherapy (no. of events)	Active treatment phase (% of affected patients)	Active treatment phase (no. of events)
Grade 1 & 2						
Leukopenia	53.3	16	66.7	62	76.7	78
Thrombocytopenia	56.7	17	50.0	46	76.7	63
Anemia	70.0	21	40.0	111	86.7	132
Infection	23.3	7	16.7	12	30.0	19
Nausea	66.7	20	46.7	39	73.3	59
Emesis	30.0	9	16.7	13	36.7	22
Polyneuropathy	30.0	9	63.3	81	70.0	81
Ototoxicity	10.0	3	23.3	33	23.3	36
Grade 3 & 4						
Leukopenia	36.7	11	66.7	68	56.7	79
Thrombocytopenia	3.3	1	36.7	33	40.0	34
Anemia	13.3	4	20.0	20	20.0	24

Infection	10.0	3	0.0	0	20.0	3
Nausea	6.7	2	0.0	0	13.3	2
Emesis	3.3	1	0.0	0	6.7	1
Polyneuropathy	16.7	5	20.0	12	26.7	12
Ototoxicity	0.0	0	20.0	1	3.3	1

Figure 1

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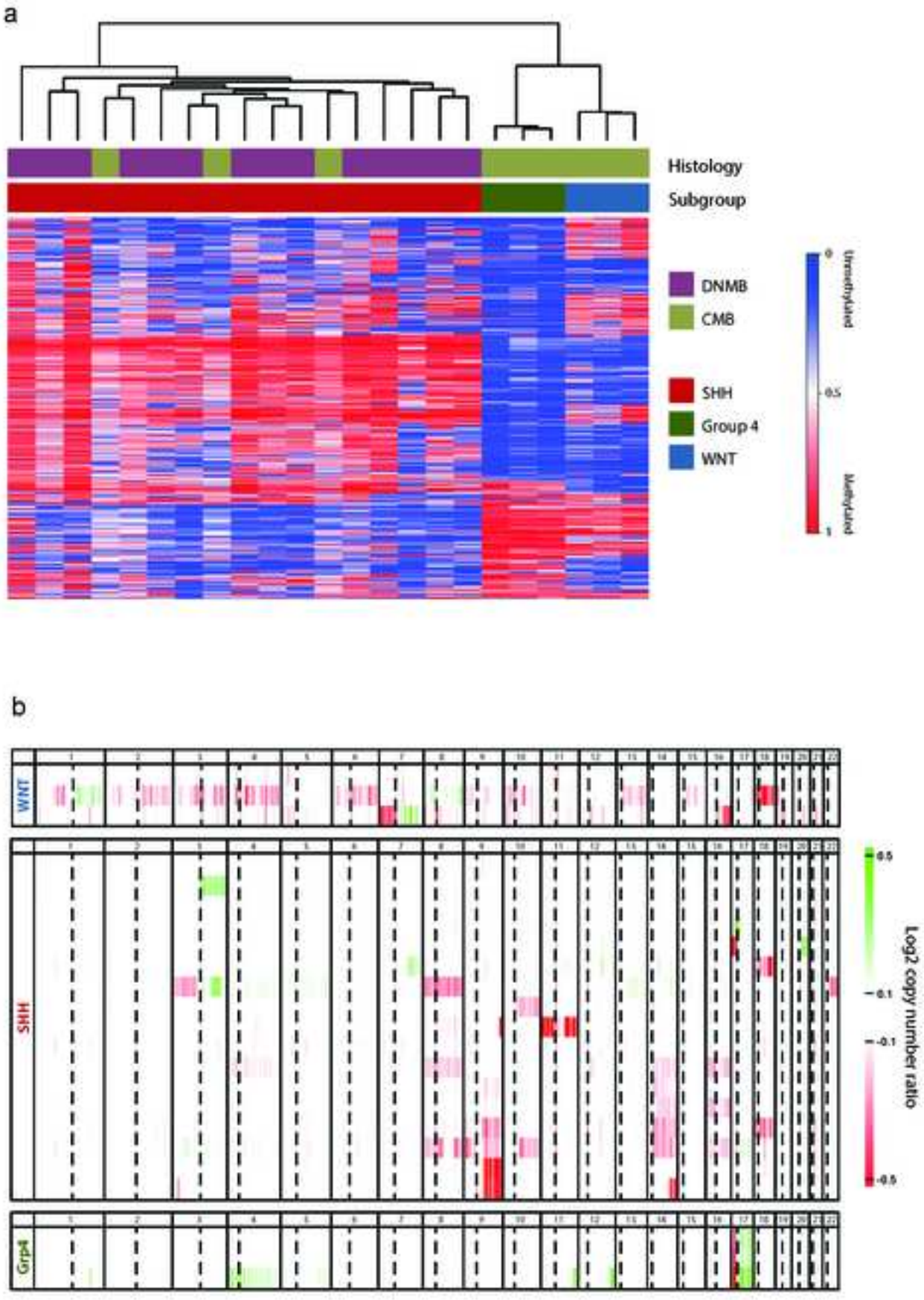

Figure 2A

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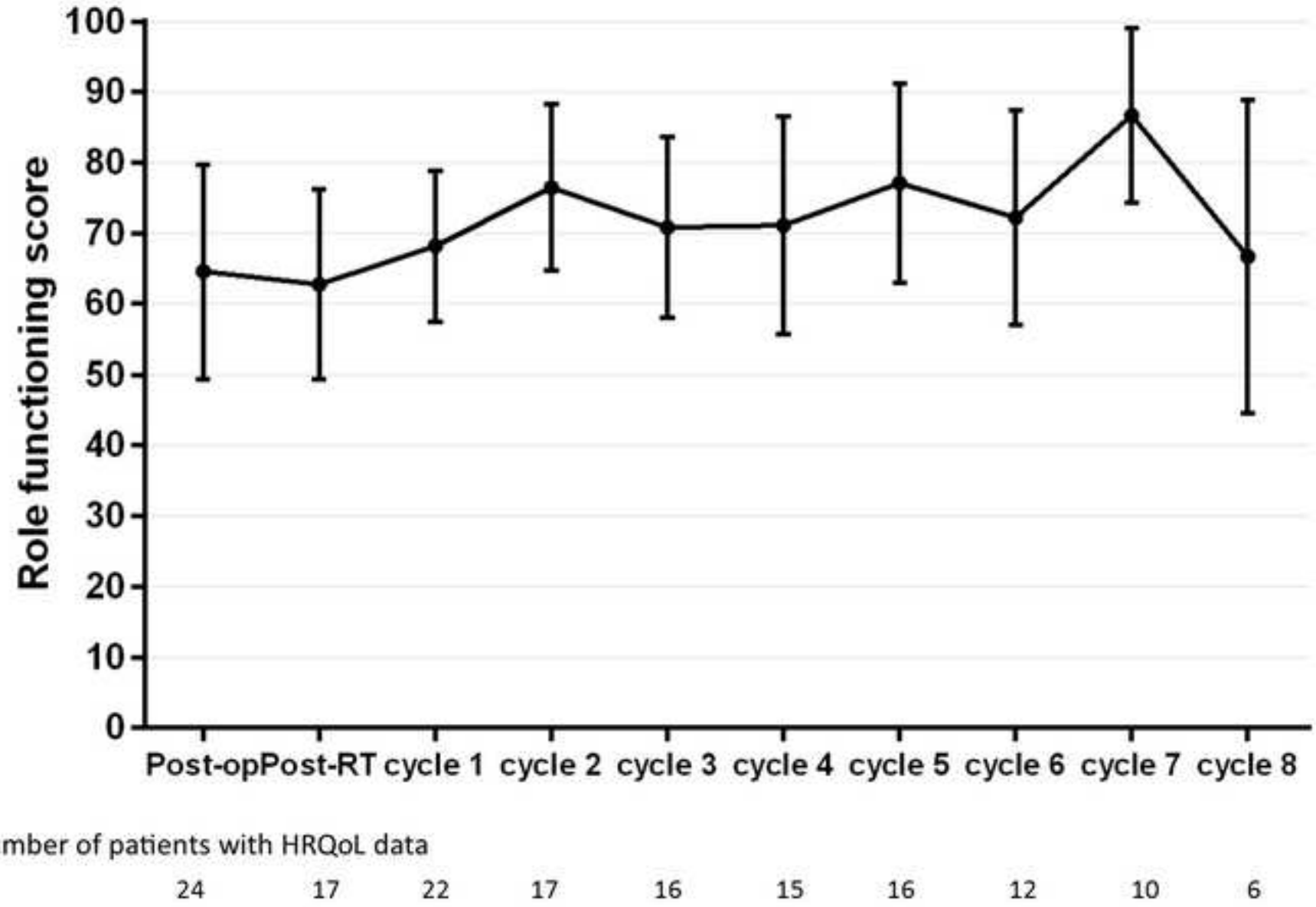

Figure 2B

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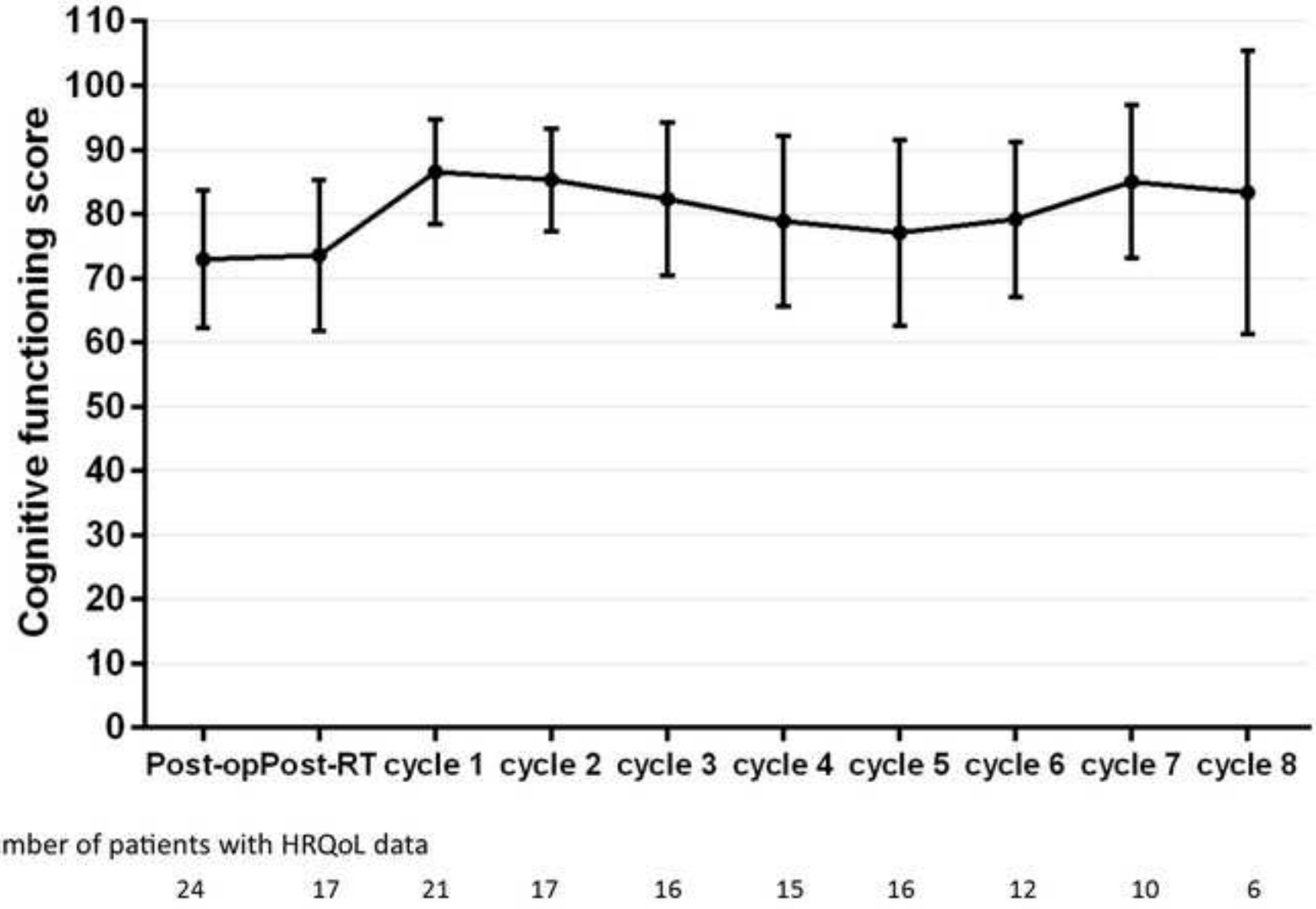

Figure 2C

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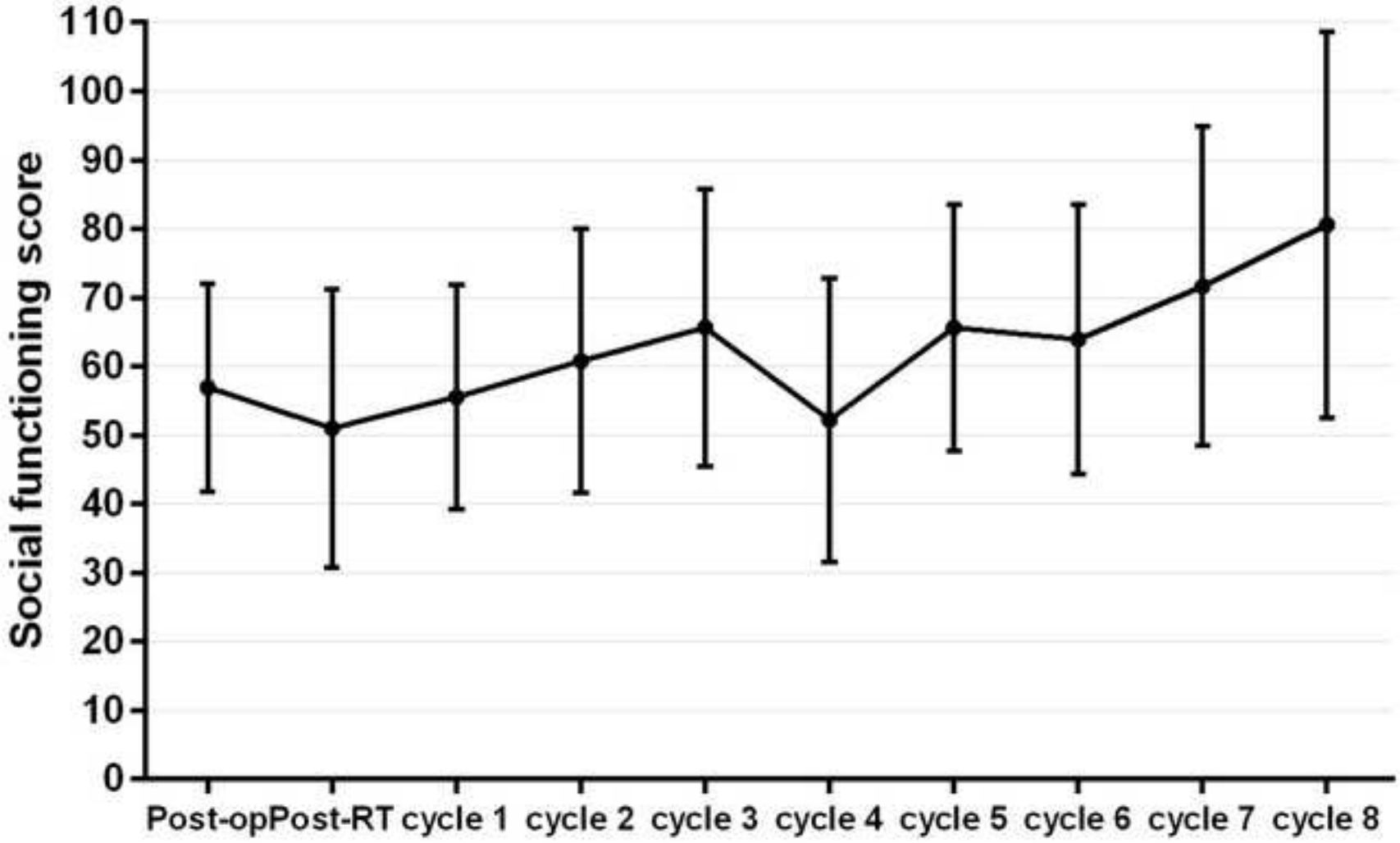

Number of patients with HRQoL data

Post-op	Post-RT	cycle 1	cycle 2	cycle 3	cycle 4	cycle 5	cycle 6	cycle 7	cycle 8
24	17	21	17	16	15	16	12	10	6

Supplementary file Figure 1

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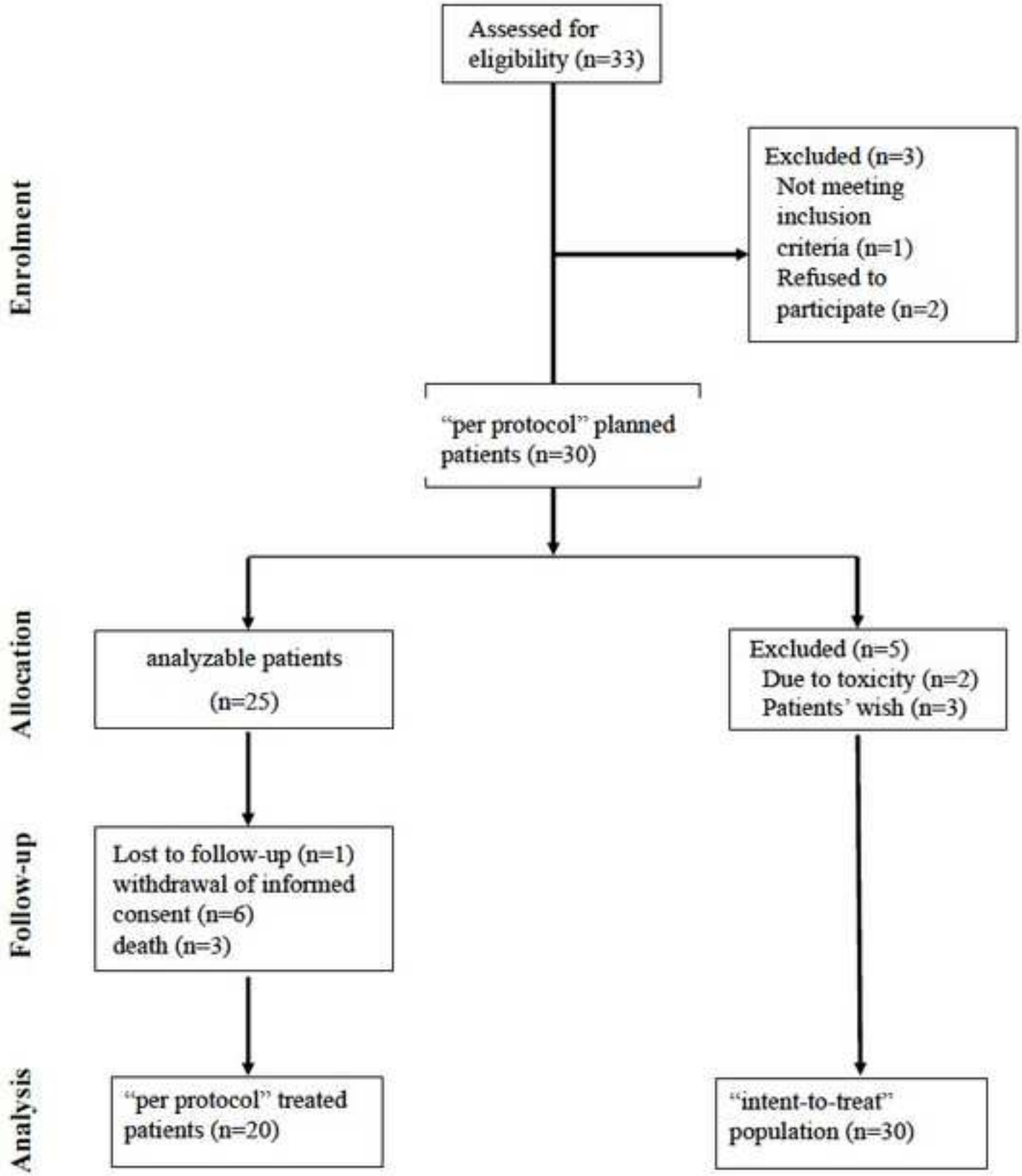
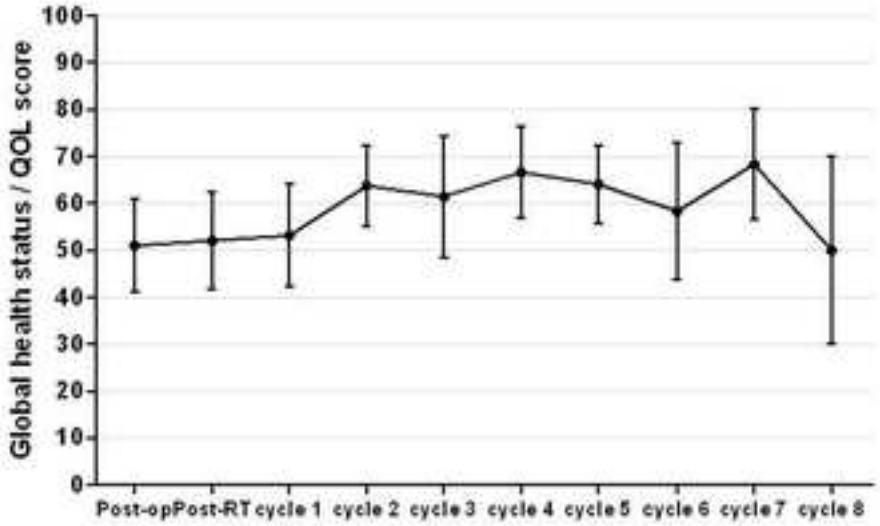


Supplementary Figure 2. Health-related quality of life (HRQoL) scores over time for the exploratory scales/items, including the number of patients with HRQoL data at each time point.

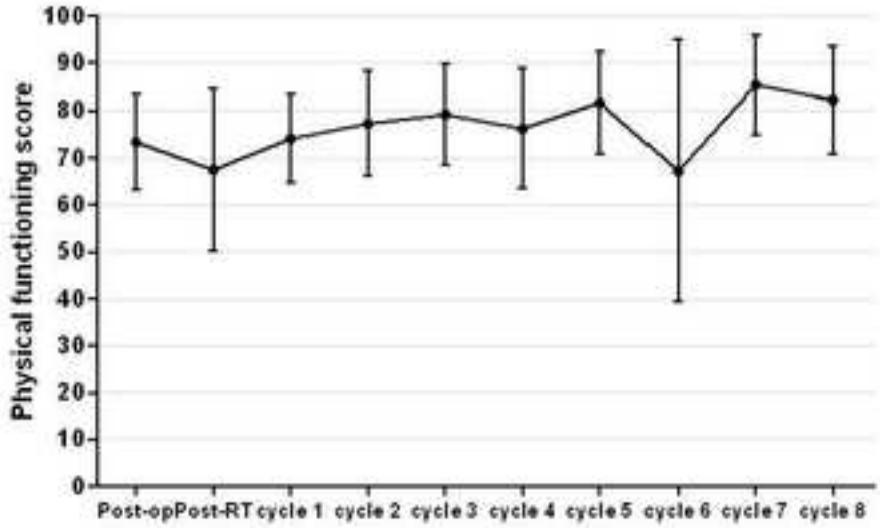
1. Global health status / QOL



Number of patients with HRQoL data

24	16	21	17	16	15	16	12	10	6

2. Physical functioning



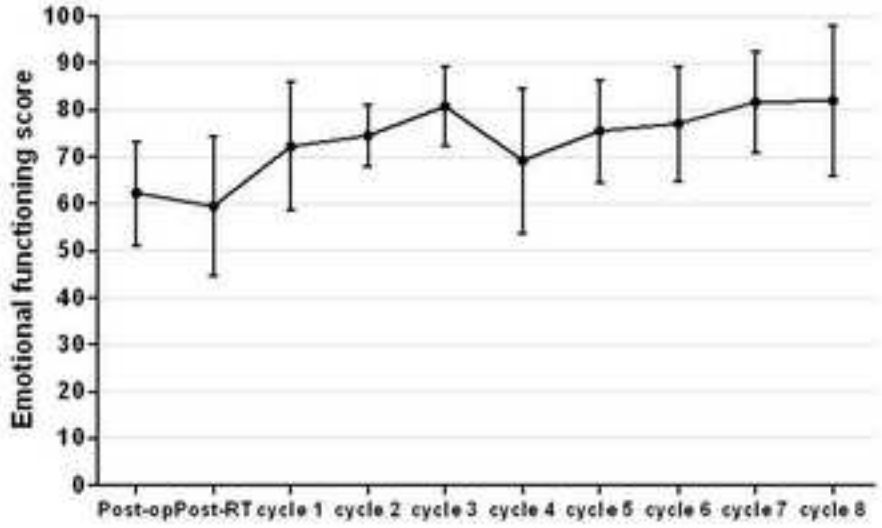
Number of patients with HRQoL data

24	17	22	17	16	15	16	12	10	6

Supplementary file Figure 3_2

Click here to download Supplementary file Suppl Fig 3_2_final_161025.tiff

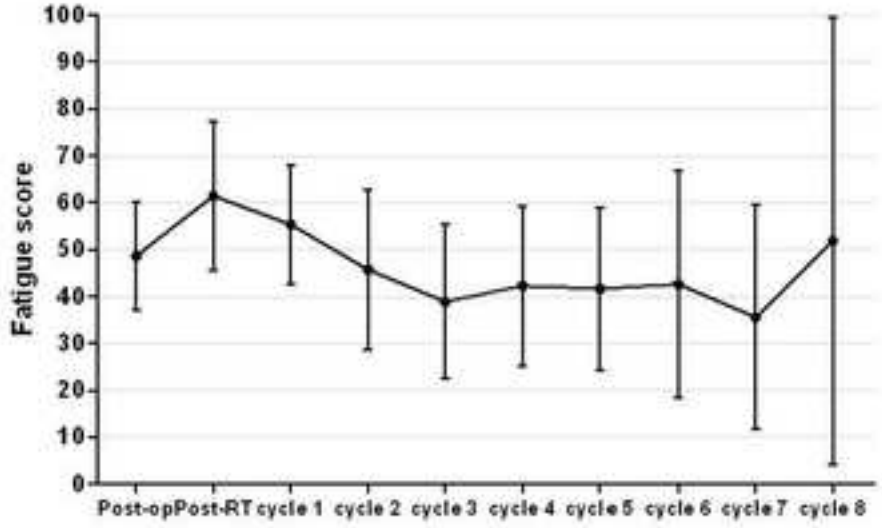
3. Emotional functioning



Number of patients with HRQoL data

24 17 21 17 16 15 16 12 10 6

4. Fatigue



Number of patients with HRQoL data

24 17 22 17 16 15 16 12 10 6

Supplementary file Figure 3_3

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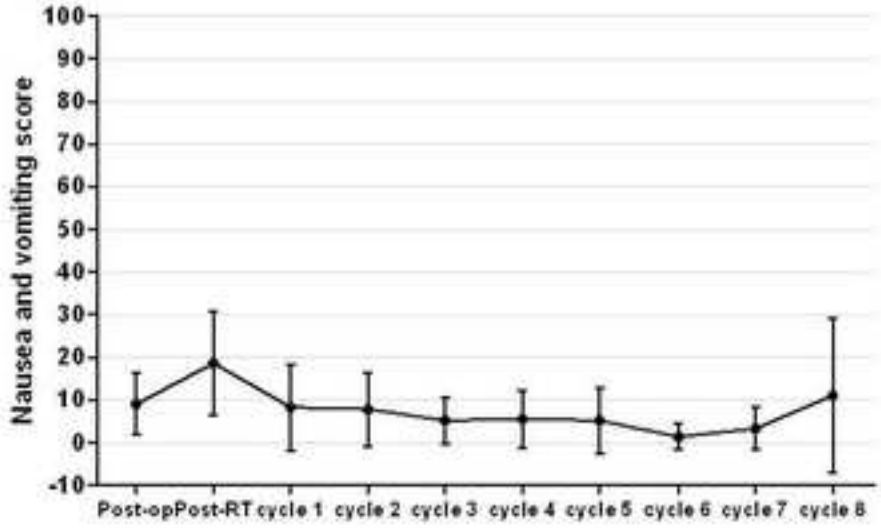
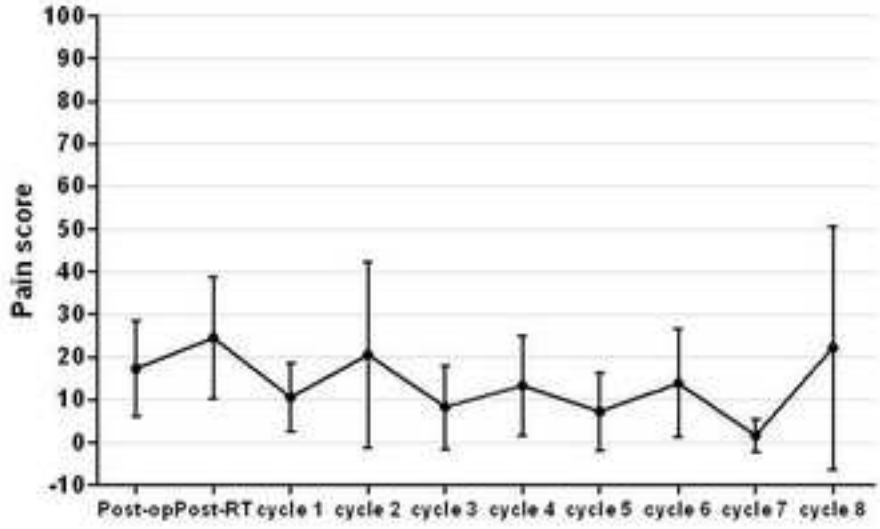
5. Nausea and vomiting



Number of patients with HRQoL data

24 17 22 17 16 15 16 12 10 6

6. Pain



Number of patients with HRQoL data

24 17 22 17 16 15 16 12 10 6

Supplementary file Figure 3_4

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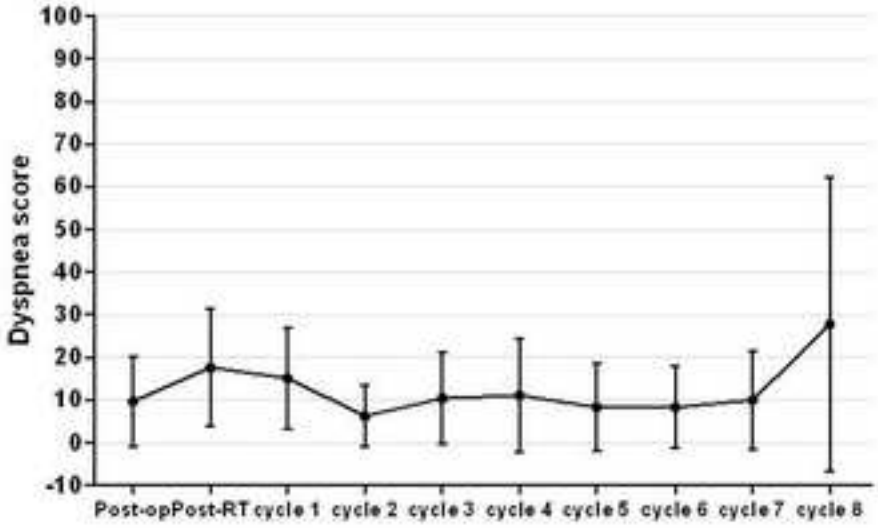
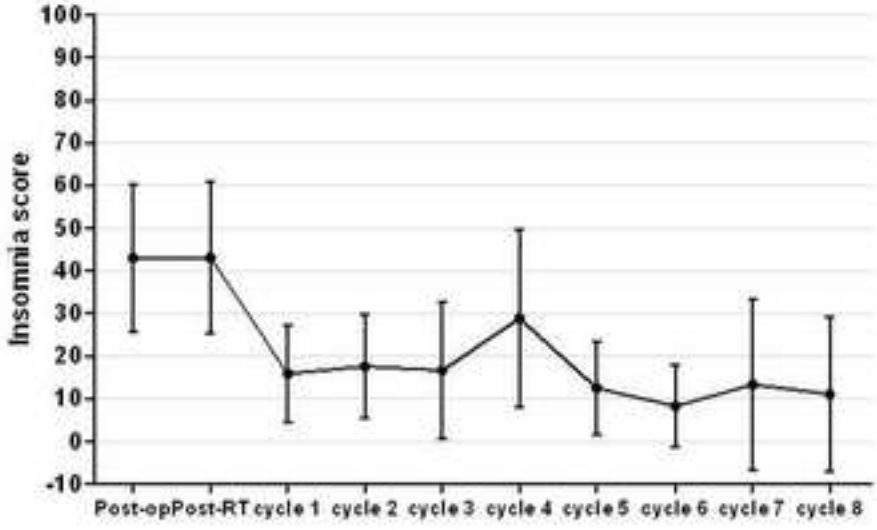
7. Dyspnea



Number of patients with HRQoL data

24 17 22 17 16 15 16 12 10 6

8. Insomnia



Number of patients with HRQoL data

24 17 21 17 16 15 16 12 10 6

Supplementary file Figure 3_5

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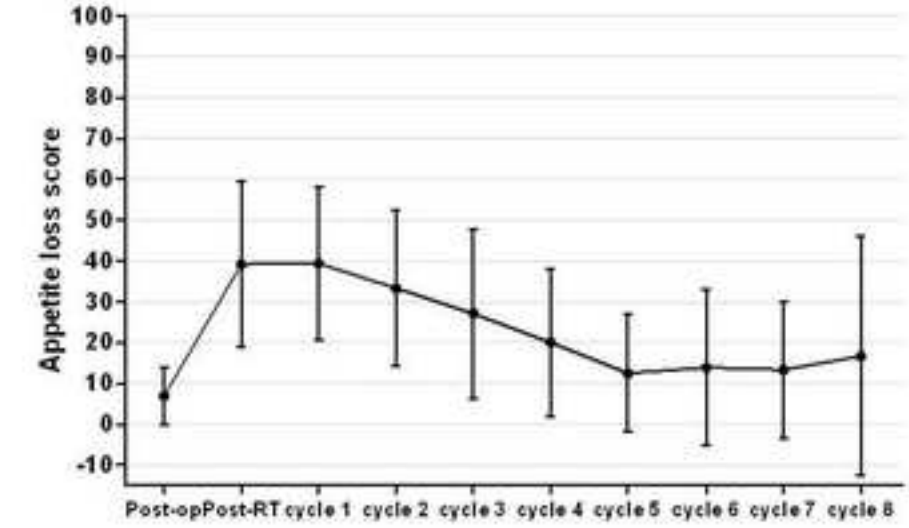
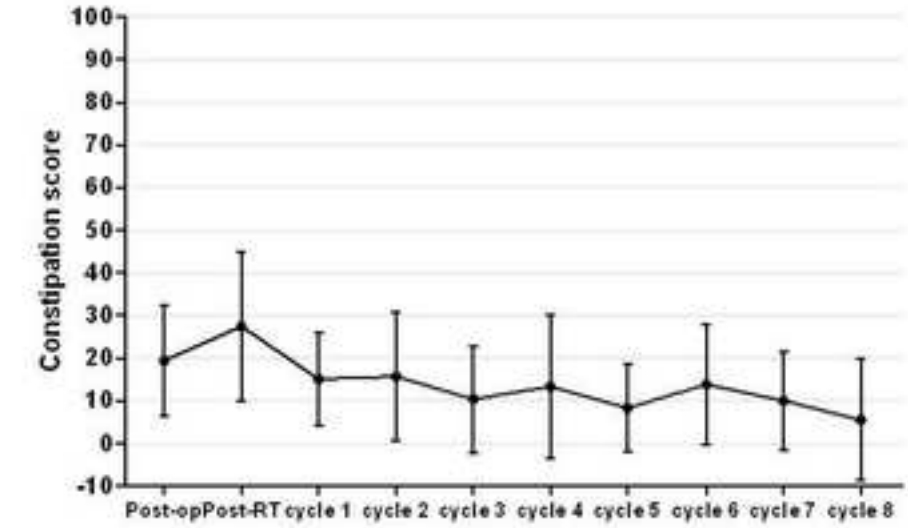
9. Appetite loss



Number of patients with HRQoL data

24 17 22 17 16 15 16 12 10 6

10. Constipation



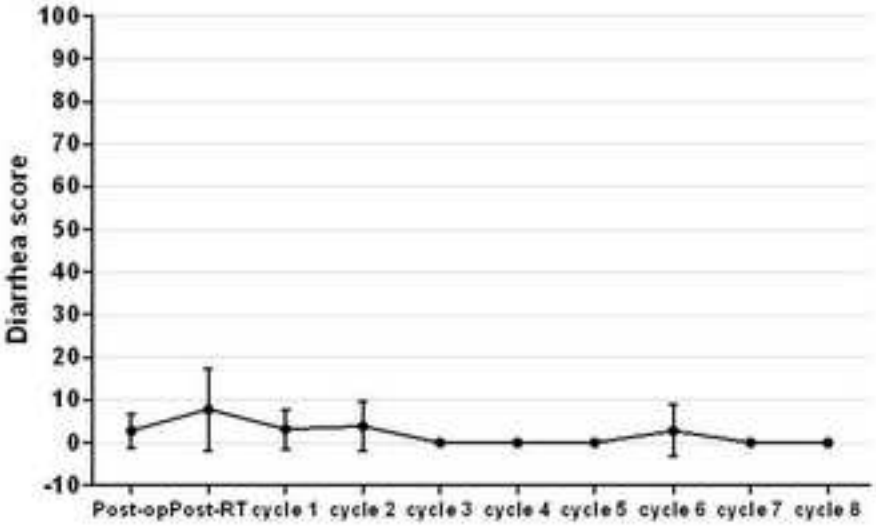
Number of patients with HRQoL data

24 17 22 17 16 15 16 12 10 6

Supplementary file Figure 3_6

Click here to download Supplementary file Suppl Fig 3_6_final_161025.tiff

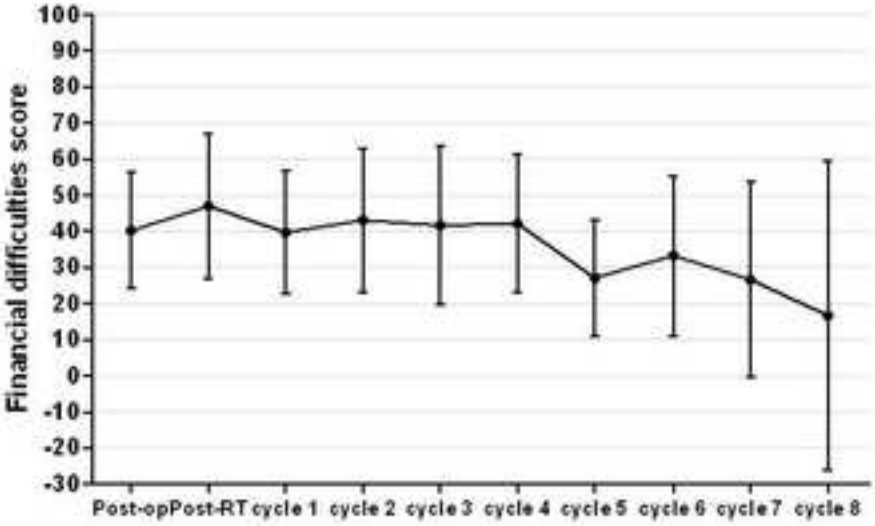
11. Diarrhea



Number of patients with HRQoL data

24 17 21 17 16 15 16 12 10 6

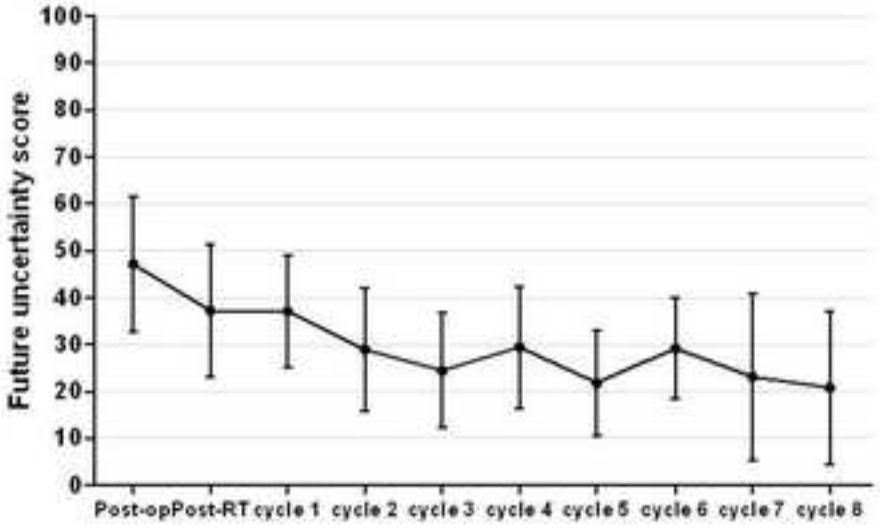
12. Financial difficulties



Number of patients with HRQoL data

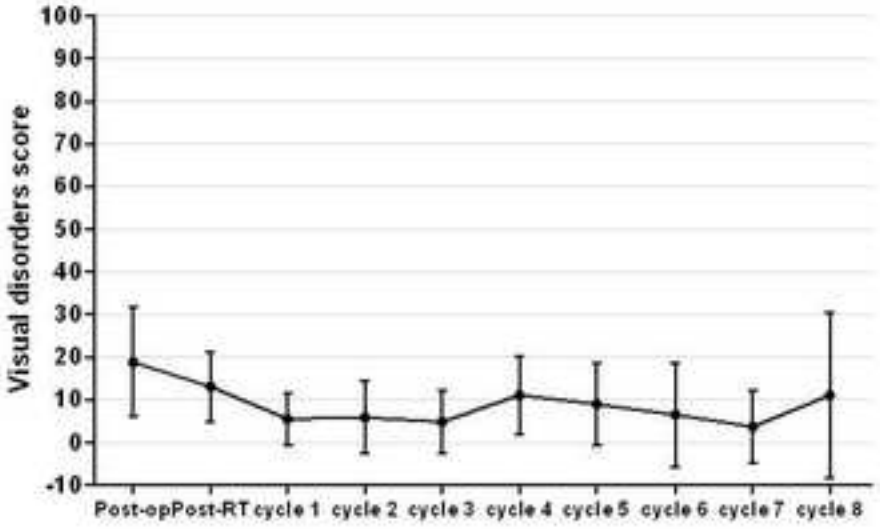
24 17 21 17 16 15 16 12 10 6

13. Future uncertainty



Number of patients with HRQoL data									
23	17	22	17	16	15	16	12	9	6

14. Visual disorders

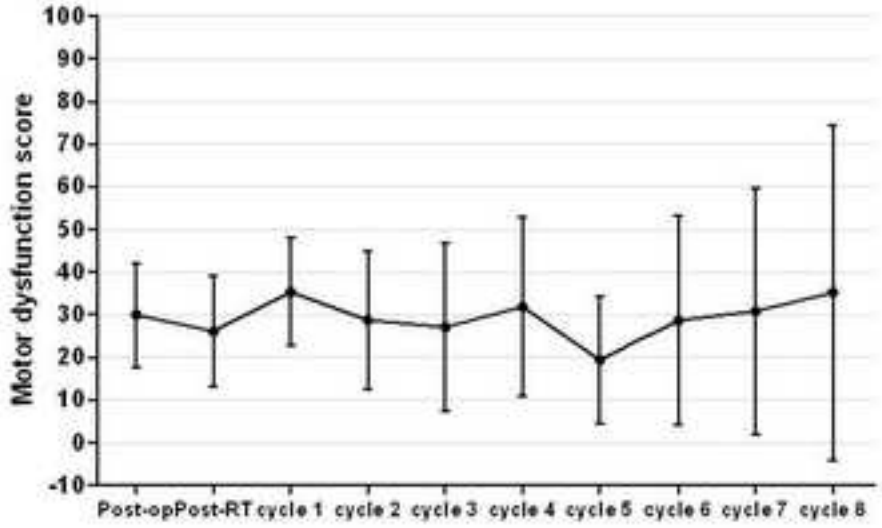


Number of patients with HRQoL data									
23	17	22	17	16	15	16	12	9	6

Supplementary file Figure 3_8

Click here to download Supplementary file Suppl Fig 3_8_final_161025.tiff

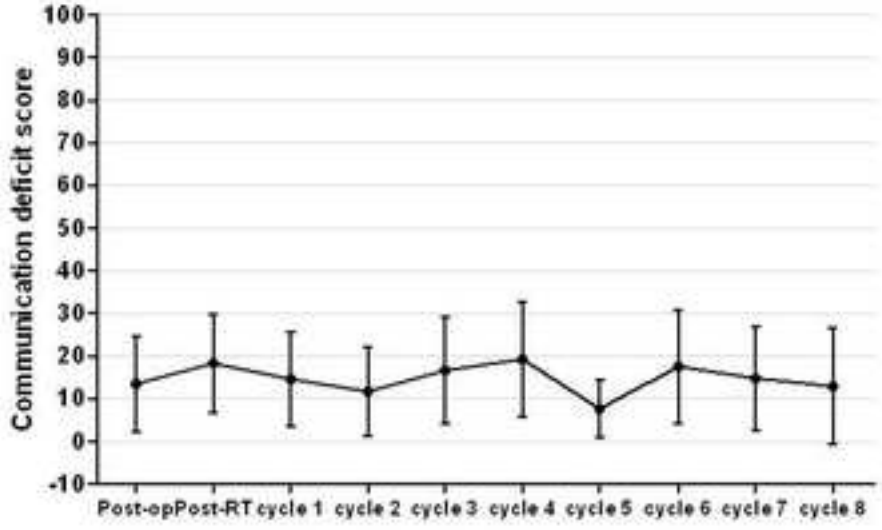
15. Motor dysfunction



Number of patients with HRQoL data

23 17 22 17 16 15 16 12 9 6

16. Communication deficit



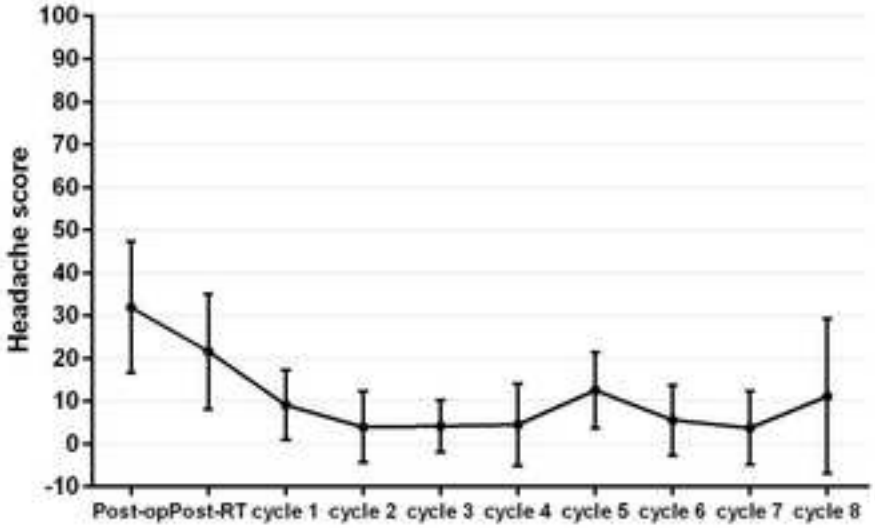
Number of patients with HRQoL data

23 17 22 17 16 15 16 12 9 6

Supplementary file Figure 3_9

Click here to download Supplementary file Suppl Fig 3_9_final_161025.tiff

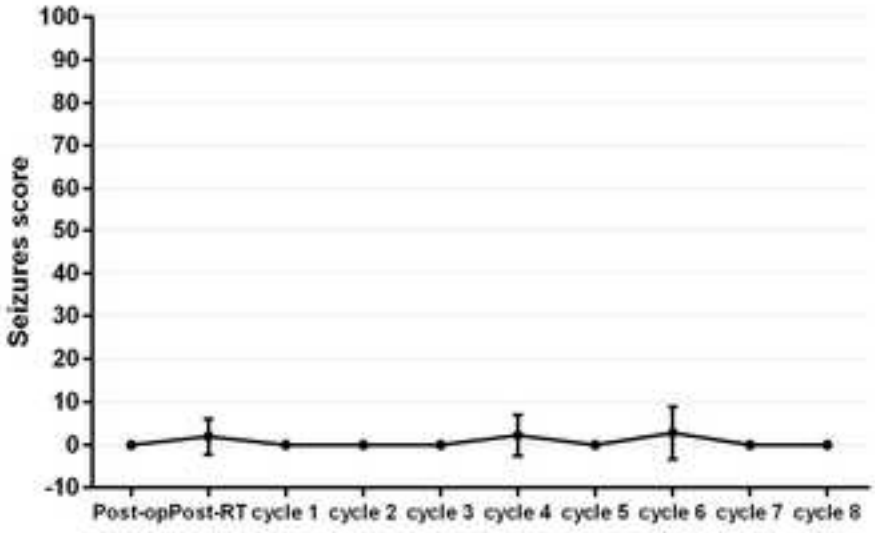
17. Headache



Number of patients with HRQoL data

23	17	22	17	16	15	16	12	9	6

18. Seizures



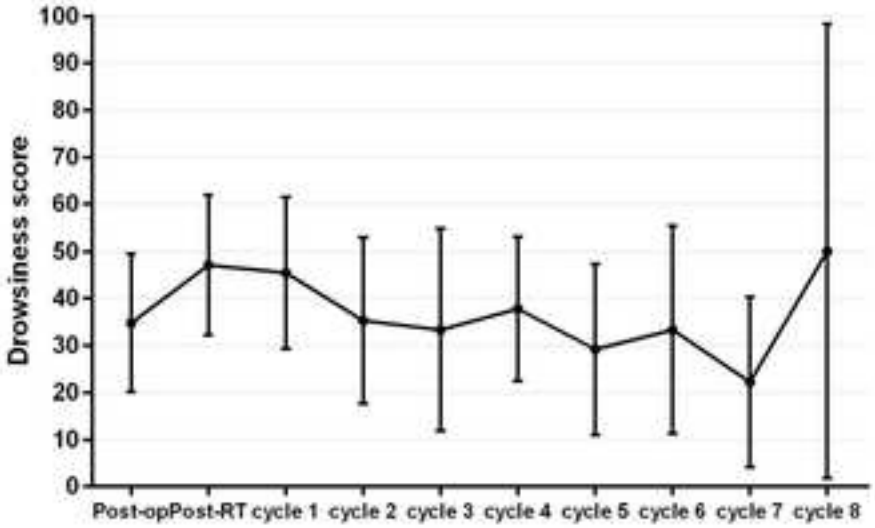
Number of patients with HRQoL data

23	17	22	17	16	15	16	12	9	6

Supplementary file Figure 3_10

Click here to download Supplementary file Suppl Fig 3_10_final_161025.tiff

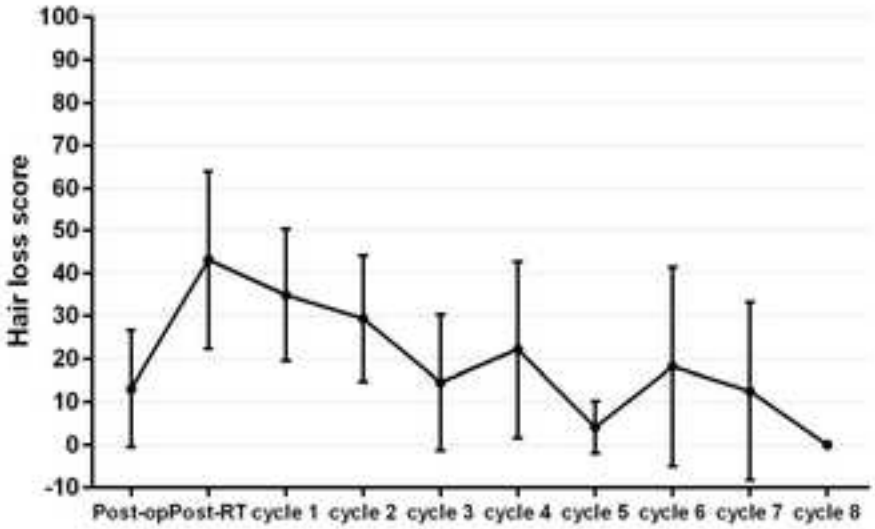
19. Drowsiness



Number of patients with HRQoL data

23	17	22	17	16	15	16	12	9	6

20. Hair loss



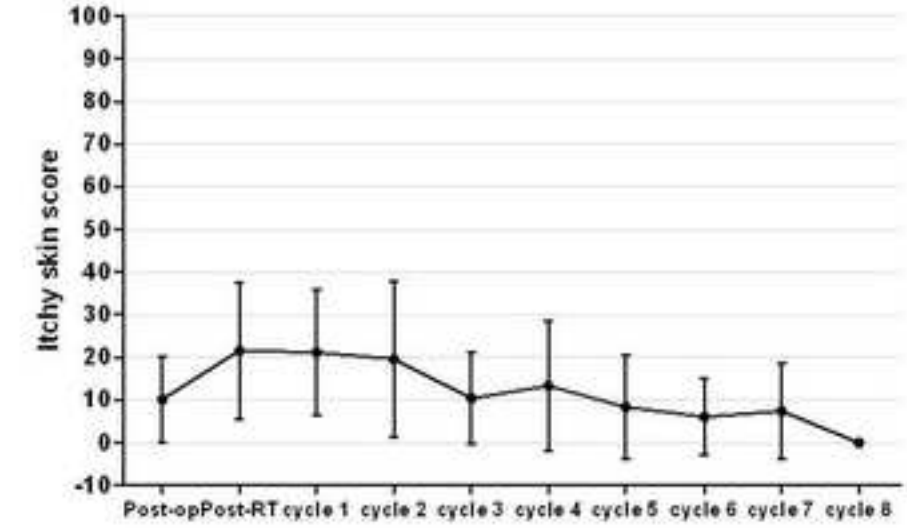
Number of patients with HRQoL data

23	17	22	17	16	15	16	11	8	5

Supplementary file Figure 3_11

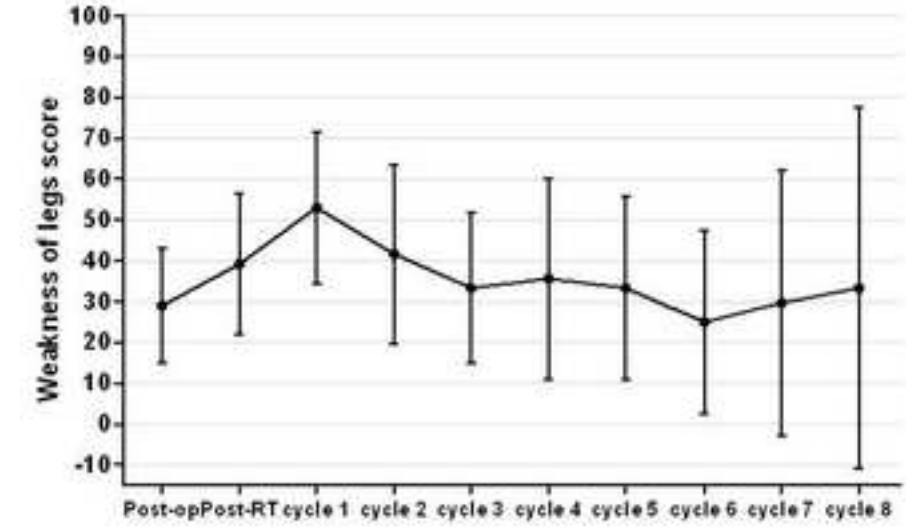
Click here to download Supplementary file Suppl Fig 3_11_final_161025.tiff

21. Itchy skin



Number of patients with HRQoL data									
23	17	22	17	16	15	16	11	9	6

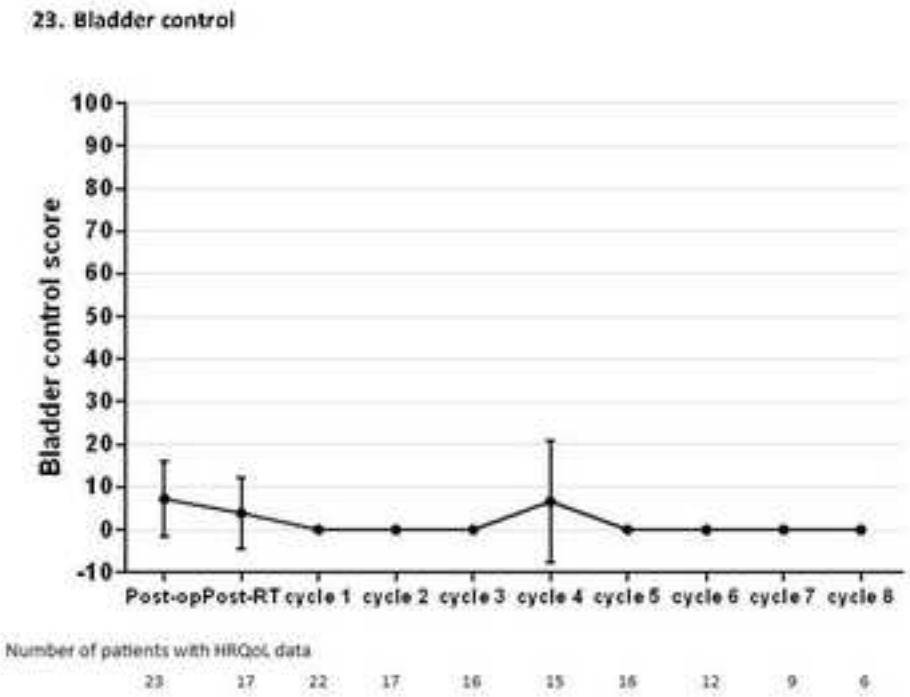
22. Weakness of legs



Number of patients with HRQoL data									
23	17	22	17	16	15	16	12	9	6

Supplementary file Figure 3_12

Click here to download Supplementary file Suppl Fig 3_12_final_161025.tiff



Suppl. Table 1 (online only)

Specific rules of dose reduction and delay. Rules for myelotoxicity, neurotoxicity, ototoxicity and nephrotoxicity were defined prospectively in the trial protocol. ANC = absolute neutrophil count; CTC = common toxicity criteria; GFR = glomerular filtration rate; G-CSF = granulocyte colony stimulating factor.

Myelotoxixity	ANC < 1500/µl AND/OR platelets < 100 000/µl	Delay treatment for one week, repeat blood analysis
	CTC° III 1000/µl < leukocytes < 2000/µl OR 500/µl < neutrophiles < 1000/µl	Dose reduction to 75% in the next cycle
	CTC° IV leukocytes < 1000/µl OR neutrophiles < 500/µl	Dose reduction to 50% in the next cycle PLUS administration of G-CSF day 5-9
Neurotoxicity	CTC° II	Reduction of Vincristine to 1 mg total dose
	CTC° III	Termination of Vincristine; if improvement to grade II, 1 mg total dose
Nephrotoxicity	GFR > 60 ml/min x 1.73m^2	Replace cisplatin by carboplatin 400 mg/m^2
	GFR < 60 ml/min x 1.73m^2	One week treatment break; if no improvement: termination of platinum-based treatment

Ototoxicity	1-3 kHz range reduction of 16-30 db	Replace cisplatin by carboplatin 400 mg/m^2
	4-8 kHz range reduction > 40 db	
	1-3 kHz range reduction > 30 db	Termination of platinum – based treatment

Suppl. Table 2 (online only)

Imaging response parameters and outcome parameters during the course of treatment and at the end of active treatment phase. P-values compare lateral vs. other localization and SSH-activated tumors vs. non-SHH-activated tumors. N.a. is not applicable.

Characteristic	Mean / range n / % of total / p-value
Tumor volume	
before treatment for enhancing tumor	14.6 cm^3 (range 0.0-37.1)
before treatment for non-enhancing tumor	25.0 cm^3 (range 0.6-38.4)
after resection	0.8 cm^3 (range 0-9.3)
after radio-chemotherapy	0.1 cm^3 (range 0-1.6)
MRI response	
Complete resection after surgery	15 (50.0%)
lateral localization	63.6%
other localizations	36.7% (p = 0.018)
SHH subgroup	45.3%
other subgroups	38.7% (p=0.026)
Resection of at least 90%	4 (13.3%)
Partial resection of any extent	8 (26.6%)

Complete response after radio-chemotherapy	22 (73.3%)

Suppl. Table 3 (online only)

Hematological and non-hematological toxicity Grade 1 & 2 and 3 & 4 in percent (%) of all treated patients during concomitant radio-chemotherapy (RCT) and adjuvant chemotherapy (cycle 1-8), Number of patients still under treatment are shown in brackets.

	RCT (n=30)	**Cycle 1 (n=25)**	**Cycle 2 (n=25)**	**Cycle 3 (n=21)**	**Cycle 4 (n=21)**	**Cycle 5 (n=21)**	**Cycle 6 (n=19)**	**Cycle 7 (n=13)**	**Cycle 8 (n=10)**
Grade 1 & 2									
Leukopenia	53·3	36·0	48·0	42·9	42·9	40·0	42·1	30·8	30·0
Thrombocytopenia	56·7	0·0	20·0	30·0	26·7	23·3	30·0	13·3	10·0
Anemia	70·0	64·0	72·0	71·4	76·2	66·7	78·9	69·2	80·0
Infection	23·3	8·0	0·0	4·8	14·3	9·5	5·3	15·4	10·0
Nausea	66·7	36·0	20·0	28·6	33·3	14·3	31·6	15·4	10·0
Emesis	30·0	16·0	4·0	9·5	9·5	4·8	15·8	0·0	0·0
Polyneuropathy	30·0	32·0	52·0	61·9	66·7	52·4	47·4	53·8	60·0
Ototoxicity	10·0	20·0	16·0	14·3	19·0	28·6	26·3	23·1	30·0
Grade 3 & 4									
Leukopenia	36·7	48·0	44·0	47·6	42·9	52·4	31·6	38·5	40·0
Thrombocytopenia	3·3	12·0	12·0	14·3	23·8	28·6	31·6	30·8	30·0
Anemia	13·3	8·0	16·0	14·3	9·5	14·3	15·8	15·4	10·0
Infection	10·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0
Nausea	6·7	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0
Emesis	3·3	0·0	0·0	0·0	0·0	0·0	0·0	0·0	0·0
Polyneuropathy	16.7	16·0	20·0	4·8	4·8	4·8	0·0	0·0	0·0

Ototoxicity	0·0	0·0	0·0	0·0	0·0	0·0	0·0	5·3	0·0

Suppl. Table 4 (online only)

Compliance (calculated as the number of received forms divided by the number of expected forms) to health-related quality of life (HRQoL) assessments during the course of treatment and at the end of the active treatment phase. *In figure 2a, b, and c, patient numbers are given with 22, 21 and 21, as one patient has not answered the respective questions in the questionnaires.

Moment of evaluation	Number of expected HRQoL forms	Number of received HRQoL forms	Compliance (%)
Post-operative	30	24	80
Post-radiotherapy	30	17	57
Cycle 1	25	22*	88
Cycle 2	24	17	71
Cycle 3	21	16	76
Cycle 4	20	15	75
Cycle 5	20	16	80
Cycle 6	18	12	67
Cycle 7	12	10	83
Cycle 8	9	6	67
End of active treatment	27	18	67

Suppl. Table 5 (online only)

Compliance (calculated as the number of received forms divided by the number of expected forms) to health-related quality of life (HRQoL) assessments during the course of treatment and at the end of the active treatment phase. *In figure 2a, b, and c, patient numbers are given with 22, 21 and 21, as one patient has not answered the respective questions in the questionnaires.

Moment of evaluation	Number of expected HRQoL forms	Number of received HRQoL forms	Compliance (%)
Post-operative	30	24	80
Post-radiotherapy	30	17	57
Cycle 1	25	22*	88
Cycle 2	24	17	71
Cycle 3	21	16	76
Cycle 4	20	15	75
Cycle 5	20	16	80
Cycle 6	18	12	67
Cycle 7	12	10	83
Cycle 8	9	6	67
End of active treatment	27	18	67

Suppl. Table 6 (online only)

Correlation analysis. Molecular subtypes were correlated to histology, molecular subtype to localization, and MRI localization to molecular subtype. Histology was available in all 30 patients, molecular subtype in 29 patients. MRI localization was not available in 4 patients due to missing source data. Significance was calculated for SHH vs. other molecular subtypes and for lateral vs. other localizations.

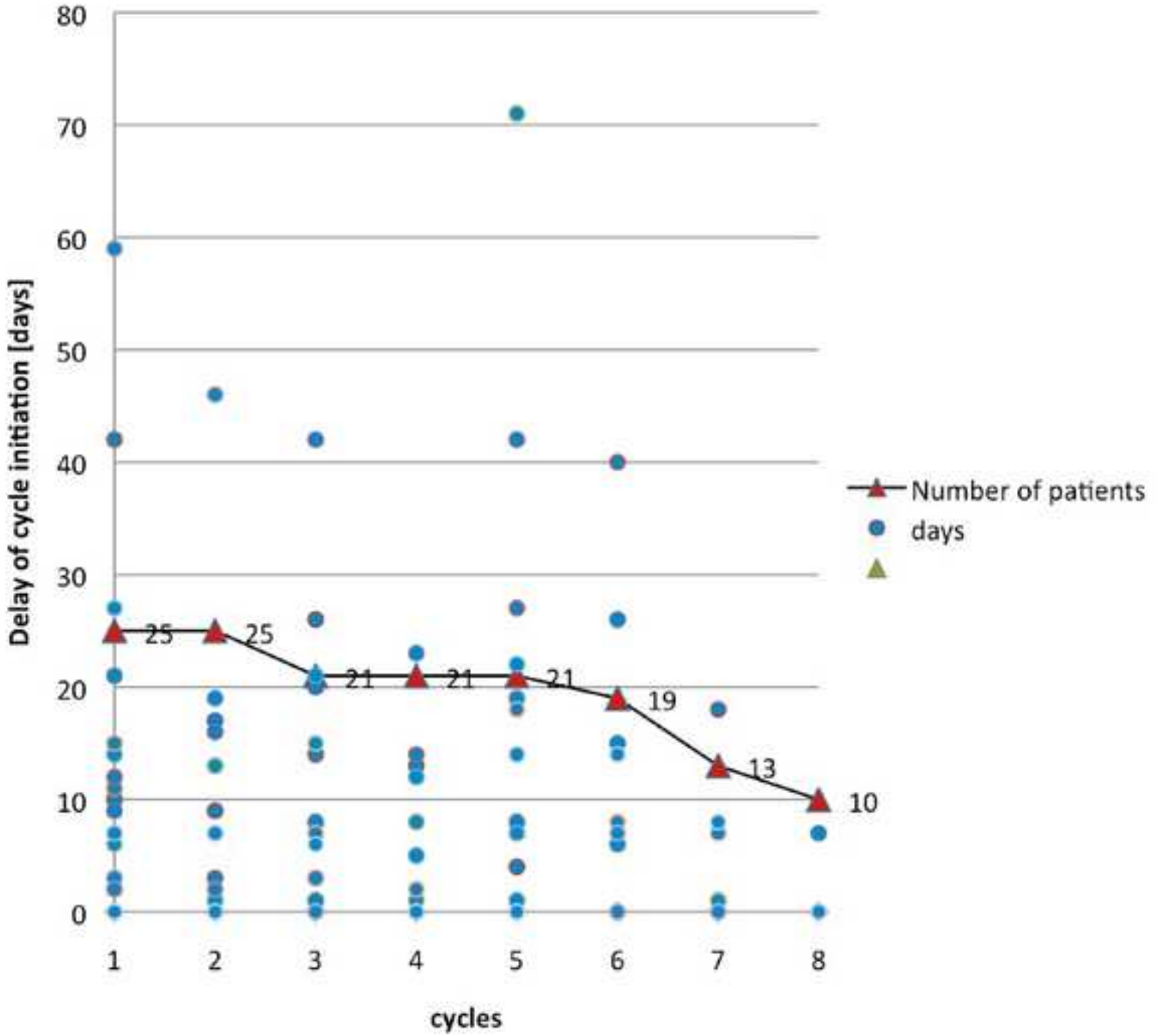
Characteristic	n (% of total; p-value)
Genetic and histological entity (n=29)	
SHH-activated	20 (66·7%)
with CMB histology	30·0%
with DNMB histology	70·0%
with MBEN histology	0·0%
WNT-activated	4 (13·3%)
with CMB histology	100·0%
with LCA histology	0·0%
Non-WNT/Non-SHH (Group 4)	5 (16·%)
with CMB histology	100·0%
with LCA histology	0·0%
Genetic entity (n=29) and MRI	

localization (n=26)	p = 0·01
SHH-activated	20 (66·7%)
lateral localization	50·0%
other localization	50·0%
WNT-activated	4 (13·3%)
lateral localization	0·0%
other localization	100·0%
Non-WNT/Non-SHH (Group 4)	5 (16·7%)
lateral localization	20·0%
other localization	80·0%
Not available	1 (3·3%)
MRI localization (n=26) and genetic entity (n=29)	p = 0·040
Lateral/hemispheric localization	11 (36·7%)
…SHH-activated	90·9%
…other subgroup	9·1%
Non-lateral localization	15 (50·0%)
SHH-activated	52·6%

other subgroup	47·4%
Not available	4 (13·3%)

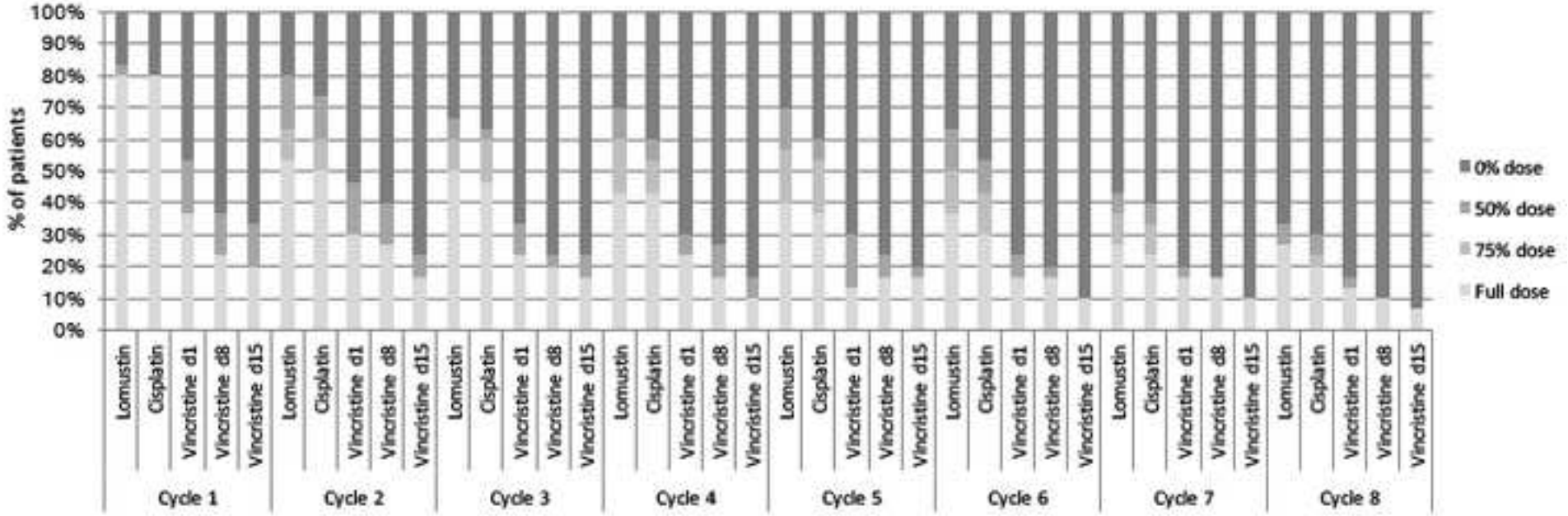
Supplementary file Figure 2A

Click here to download Supplementary file Suppl Fig 2A_final_170601.tiff



Supplementary file Figure 2B

Click here to download Supplementary file Suppl Fig 2B_final_170506.tiff



Supplementary Table and Figure Legends

Suppl. Figure 1 (online only)

CONSORT statement flow diagram.

Suppl. Figure 2 (online only)

Treatment delay during adjuvant chemotherapy. Treatment delay is shown in average in days and for individual cycles of chemotherapy. Treatment was delayed for 10 days in average, and 70 days in maximum (A). Amount of dose de-escalation for each substance. Vincristine was stopped early on in a high number of patients, whereas lumustine and cisplatin were first de-escalated, and typically stopped later. Data show numbers of patients with 0% of dose (corresponding to termination of the respective substance), and 50%, 75%, and full dose per substance per cycle (B). D = day.

Suppl. Figure 3 (online only)

Health-related quality of life (other than main categories). Scores over time for the exploratory scales/items, including the number of patients with HRQoL data at each time point.

Suppl. Figure 4 (online only)

Lexical and semantic verbal fluency. Scores over time after resection (time point 1 = TP1), after radio-chemotherapy (time point 2 = TP2), and after adjuvant therapy (time point 3 = TP3) are shown.

Suppl. Table 1 (online only)

Specific rules for dose de-escalation and delay. Rules for myelotoxicity, neurotoxicity, ototoxicity and nephrotoxicity were defined prospectively in the trial protocol. ANC = absolute neutrophil count; CTC = common toxicity criteria; GFR = glomerular filtration rate; G-CSF = granulocyte colony stimulating factor.

Suppl. Table 2 (online only)

Imaging response parameters and outcome parameters during the course of treatment and at the end of active treatment phase. P-values compare lateral vs. other localization and SSH activated tumors vs. non-SHH-activated tumors. N.a. is not applicable.

Suppl. Table 3 (online only)

Hematological and non-hematological toxicity Grade 1 & 2 and 3 & 4 in percent (%) of all treated patients during concomitant radio-chemotherapy (RCT) and adjuvant chemotherapy (cycle 1-8), Number of patients still under treatment are shown in brackets.

Suppl. Table 4 (online only)

Compliance (calculated as the number of received forms divided by the number of expected forms) to health-related quality of life (HRQoL) assessments during the course of treatment and at the end of the active treatment phase. *In figure 2a, b, and c, patient numbers are given with 22, 21 and 21, as one patient has not answered the respective questions in the questionnaires.

Suppl. Table 5 (online only)

Postoperative Health-Related Quality of Life (HRQoL) scores for the preselected scales and the exploratory scales/items (scales: higher scores mean better functioning, items: higher

scores mean more problems), separately for medulloblastoma patients, the general population and newly diagnosed glioblastoma patients.

Suppl. Table 6 (online only)

Correlation analysis. Molecular subtypes were correlated to histology, molecular subtype to localization, and MRI localization to molecular subtype. Histology was available in all 30 patients, molecular subtype in 29 patients. MRI localization was not available in 4 patients due to missing source data. Significance was calculated for SHH vs. other molecular subtypes and for lateral vs. other localizations.